



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 62

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 62

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Volume 62



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Contents

CONTRIBUTORS	vii
PREFACE	ix

N-Fluoropyridinium Salts

LUCJAN STREKOWSKI AND ALEXANDER S. KISELYOV

I. Introduction	1
II. Synthesis	2
III. General Properties and Spectra	3
IV. Reactivity	4
V. Future Perspectives	14
References	15

New Developments in the Chemistry of Pyrans

J. KUTHAN, P. ŠEBEK, AND S. BÖHM

I. Introduction	20
II. Nomenclature	20
III. Synthesis from Acyclic Precursors	20
IV. Synthesis from Cyclic Precursors	51
V. Reactions	68
VI. Physical Properties and Theoretical Chemistry	111
VII. Other Properties	120
References	121

The Chemistry of Dithiadiazolylium and Dithiadiazolyl Rings

JEREMY M. RAWSON, ARTHUR J. BANISTER, AND IAN LAVENDER

Foreword	140
I. Introduction: Dithiadiazolyls, New Members of an Old Class of Free Radicals	142

II. Synthetic Approaches to the 1,2,3,5-Dithiadiazolylium Cation	146
III. Theoretical Studies of 1,2,3,5-Dithiadiazolylium Heterocycles	154
IV. Physical Properties of Mono-1,2,3,5-Dithiadiazolylium Salts	158
V. X-Ray Diffraction Studies of Mono-1,2,3,5-Dithiadiazolylium Salts	162
VI. Reactions of 1,2,3,5-Dithiadiazolylium Salts	170
VII. Preparation of 1,2,3,5-Dithiadiazolyls	174
VIII. Theoretical Studies of 1,2,3,5-Dithiadiazoyl Radicals	175
IX. Physical Properties of 1,2,3,5-Dithiadiazoyl Radicals	177
X. Electron and X-Ray Diffraction Studies of 1,2,3,5-Dithiadiazoyl Radicals	183
XI. Reactivity of 1,2,3,5-Dithiadiazoyl Radicals	189
XII. Preparation of Mono-1,3,2,4-Dithiadiazolylium Salts	195
XIII. Theoretical Studies of 1,3,2,4-Dithiadiazolylium Salts	201
XIV. Physical Properties of 1,3,2,4-Dithiadiazolylium Salts	202
XV. X-Ray Diffraction Studies of 1,3,2,4-Dithiadiazolylium Salts	205
XVI. Reactivity of 1,3,2,4-Dithiadiazolylium Salts	206
XVII. Preparation of 1,3,2,4-Dithiadiazolyls	209
XVIII. Physical Properties of 1,3,2,4-Dithiadiazolyls	210
XIX. Theoretical Studies of 1,3,2,4-Dithiadiazoyl Radicals	213
XX. X-Ray Diffraction Studies of 1,3,2,4-Dithiadiazolyls	214
XXI. Reactivity of 1,3,2,4-Dithiadiazolyls	216
XXII. Multi-1,2,3,5-Dithiadiazolylium Salts and Dithiadiazolyls	219
XXIII. Multi-1,3,2,4-Dithiadiazolylium Salts and Dithiadiazolyls	227
XXIV. Mixed 1,3,2,4-/1,2,3,5-Dithiadiazolylium Salts and Related Free Radicals	236
XXV. Conclusions	240
References	240

The Reactivity of Tetrathia- and Tetraselenafulvalenes

JAVIER GARÍN

I. Introduction and Scope	249
II. Reactivity of Tetrathiafulvalenes	251
III. Reactivity of Tetraselenafulvalenes	292
References	296

Organometallics in Coupling Reactions in π -Deficient Azaheterocycles

KJELL UNDHEIM AND TORE BENNECHE

I. Introduction	306
II. Cross-Coupling by Hydrogen Substitution	307
III. Cross-Coupling by Metal Substitution	330
IV. Homo-Coupling	406
References	412

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Preface

Volume 62 of our series consists of five chapters. *N*-Fluoropyridinium salts were first obtained less than ten years ago, but have proved to be of great interest from the point of view of their unique stability, reactivity, and because they offer highly interesting possibilities in synthesis. L. Strekowski and A. S. Kiselyov (Georgia State University) have now provided the first available review of the reactions and properties of this novel class.

Pyran chemistry was reviewed in Volume 34 in our series in 1983 by J. Kuthan; he and his group (J. Kuthan, P. Šebek and S. Böhm of the Prague Institute of Chemical Technology, Czech Republic) have now updated that overview. The present chapter follows on the corresponding thia-, seleno-, and telluro-analogs, which appeared in Volume 59 of *Advances* in 1994.

The third contribution in our volume reviews the interesting classes of five-membered heterocyclic rings containing two sulfur and two nitrogen atoms, both as anionic and radical species. This area lies on the border of organic and inorganic chemistry; since its inception, in 1977, it made great strides as are now documented by J. M. Rawson, A. J. Banister, and I. Lavender of the University of Durham, UK.

Tetrathia- and tetraselenafulvalenes have become of increasing interest as organic materials: the organic chemistry and synthesis of these compounds is now covered by J. Garín (University of Zaragoza, Spain).

Coupling reactions catalyzed by palladium and involving tin, boron and other organometallic derivatives have become of increasing importance in all areas of organic chemistry. K. Undheim and T. Benneche (University of Oslo, Norway) have now reviewed these reactions with reference to their application to π -deficient azaheterocycles.

A. R. KATRITZKY

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N-Fluoropyridinium Salts

LUCJAN STREKOWSKI AND ALEXANDER S. KISELYOV

*Department of Chemistry, Georgia State University,
Atlanta, Georgia*

I. Introduction	1
II. Synthesis	2
III. General Properties and Spectra	3
IV. Reactivity	4
A. Mechanistic Aspects	4
B. Fluorination Reactions	5
1. General Remarks	5
2. Aromatic Compounds	5
3. Heterocyclic Compounds	6
4. Other Derivatives	7
C. Reactions at the Pyridinium Ring System	9
1. Nucleophile Additions	9
2. Base-Mediated Transformations	12
3. Homolytic Reactions	13
V. Future Perspectives	14
References	15

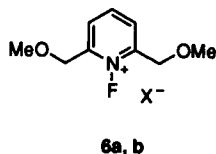
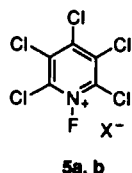
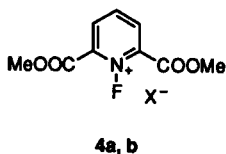
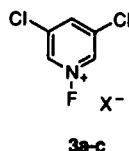
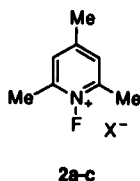
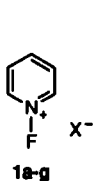
I. Introduction

The reaction of pyridine with molecular fluorine to give 2-fluoropyridine in low yield was first observed by Simons (50MI1). Historically, it was Meinert (65ZC64) who for the first time isolated an intermediate fluorine-pyridine adduct by bubbling elemental fluorine through a solution of pyridine (Py) in CFCl_3 at -80°C . The white precipitate of apparent structure $[\text{PyF}]^+\text{F}^-$ decomposed violently upon heating to -2°C to give a red-brown oil containing 2-fluoropyridine (83IZV2655). The suggested formation of an unstable *N*-fluoropyridinium cation $[\text{PyF}]^+$ was in sharp contrast to the well-known generation of a molecular complex or a stable dicoordinated halogen cation $[\text{Py}_2\text{X}]^+$ by the reaction of chlorine, bromine, or iodine with pyridine (57PCS250; 73MI1; 90JOC3104). The apparently different reactivity of fluorine was discussed in terms of the highest electronegativity of the fluorine atom, its high oxidation potential, low polarizability, the lack of *d*-orbitals, and extremely poor two-coordinating ability (74MI1; 83MI1). The *N*-fluoropyridinium cation was not characterized for

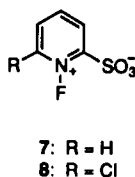
the next two decades until Umemoto and Tomita (86TL3271) obtained stable *N*-fluoropyridinium salts. Their report resulted in a renewed interest in the chemistry of the *N*-fluoropyridinium cation. A substantial volume of primary chemical literature has appeared through February 1994 to warrant this first review.

II. Synthesis

It was reasoned that the instability of the fluorine–pyridine complex of apparent structure **1a** is due to the high nucleophilicity and/or basicity of the fluoride anion toward the *N*-fluoropyridinium cation (86TL3271). This assumption proved to be correct, and a large number of stable salts, all of which contained a relatively nonnucleophilic and nonbasic counteranion, were prepared. Selected examples (**1–6**) (86TL3271; 89JOC1726; 90OS129; 93T2151) and internal salts (**7, 8**) (90JA8563) are shown.



a-g	X
a	F
b	CF ₃ SO ₃
c	BF ₄
d	PF ₆
e	SbF ₆
f	ClO ₄
g	<i>n</i> -C ₄ F ₉ SO ₃



Most conveniently, pyridinium salts (**1**–**6**) are prepared by bubbling elemental fluorine through a solution of the corresponding pyridine and an inorganic salt, such as $\text{CF}_3\text{SO}_3\text{Na}$, LiBF_4 , NaPF_6 , NaSbF_6 , or LiClO_4 , in dry acetonitrile at low temperature. Workup includes filtration of inorganic materials, concentration, and crystallization of **1**–**6** from acetonitrile. Modified procedures involve generation of a pyridinium fluoride (**1a**–**6a**) followed by treatment with the inorganic salt or treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in the preparation of a tetrafluoroborate salt. A triflate salt (**1b**–**6b**) can also be prepared directly by the reaction of an *N*-(trimethylsilyl)pyridinium triflate with elemental fluorine in acetonitrile at -40°C (86TL3271). Although all these procedures involve work with fluorine, a highly toxic gas and a strong oxidant, the preparations are safe if standard precautions are followed (89H249; 90OS129; 93T2151). Elemental fluorine diluted with argon or nitrogen for safety is available commercially.

III. General Properties and Spectra

The *N*-fluoropyridinium salts are crystalline species with melting points ranging from 90°C for **1c** to above 300°C for **1e** (86TL3271). With the notable exception of perchlorates, such as **1f**, they are shock-resistant, thermally stable, and nonhygroscopic. Care must be taken in work with the perchlorates because in dry form they can undergo a violent explosion if touched, even with a soft Teflon spatula (94UP1).

The salts are stable indefinitely when stored under strictly anhydrous conditions. The solutions in dry degassed dichloromethane, tetrahydrofuran, or acetonitrile are also relatively stable. The salts undergo a slow decomposition when dissolved in dimethyl sulfoxide, *N,N*-dimethylformamide, alcohols, or water (94UP1). For example, a half-life of 13 days for the triflate **1b** in D_2O at room temperature has been reported (90OS129). Tertiary amine-mediated decomposition is rapid at room temperature.

In contrast to the cyclovoltammetric and polarographic reversible reduction of *N*-alkyl pyridinium salts to the corresponding radical (89JA5185), the electrochemical reduction of *N*-fluoropyridinium salts is irreversible (92T1595). Theoretical calculations strongly suggest the initial electron transfer to the π -system rather than to the nitrogen–fluorine bond (94UP2). Facile reduction is consistent with the high oxidation power of *N*-fluoropyridinium salts. Oxidation of colorless iodide ion to elemental iodine in the presence of starch to enhance the color of iodine is widely used as a convenient test for the presence of *N*-fluoropyridinium salts (90TL7379).

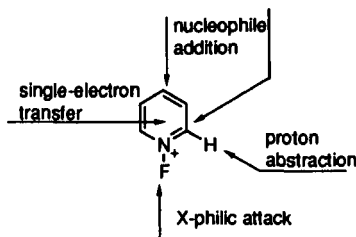
The stability of the nitrogen–fluorine bond (58MI1) and the nature of the *N*-fluoropyridinium cation have been discussed in terms of back-

donation of *p*-electrons on the fluorine atom to the positive ring nitrogen (69MI1). The ^1H and ^{19}F NMR spectra are fully consistent with the presence of a free cation. This conclusion comes primarily from the analysis of the spectra of **1b–g** containing different counteranions. In particular, the fluorine chemical shift $\delta = 48.6 \pm 0.2$ in CD_3CN with CFCl_3 as internal standard has been noted for all derivatives (**1b–g**). The ^{19}F chemical shifts are sensitive to substituents at the pyridinium ring. Electron-donating groups cause upfield shifts, and the presence of electron-withdrawing groups results in deshielding. The only known exception is the cation of **4**, in which the two methoxycarbonyl groups in the vicinity of the fluorine cause an upfield shift to $\delta = 25.5$, apparently as a result of the anisotropic effect of the carbonyl groups (86TL3271; 89JOC1726). The mass spectra obtained by the SIMP method show a molecular ion peak corresponding to *N*-fluoropyridinium cation as the most intense peak (86TL3271; 94UP1).

IV. Reactivity

A. MECHANISTIC ASPECTS

The *N*-fluoropyridinium cation is a multicenter electrophile with several potential sites for reactions with nucleophiles or bases (Scheme 1). The X-philic attack at the fluorine atom is analogous to S_N2 substitution at a carbon atom, and it has been suggested to be operative in fluorination of nucleophilic species by *N*-fluoropyridinium salts (82CRV615; 92T1595). However, evidence has been accumulating recently that the single-electron transfer (SET) process may be the major reaction pathway in the fluorination of a vast majority of organic substrates (90JA8563; 92T1595). Single-electron transfer, nucleophile addition, and proton abstraction are all important processes in the syntheses of substituted pyridines. The charge concentration at the pyridinium nitrogen atom may be responsible



SCHEME 1

for the preferential addition of nucleophile at the 2 position observed in a vast majority of known cases as well as the exclusive proton abstraction at this position of the *N*-fluoropyridinium cation. Synthetically useful transformations that have been suggested to involve these mechanistic pathways are discussed in the following sections.

B. FLUORINATION REACTIONS

1. General Remarks

Recently, reagents and methods for selective introduction of fluorine into organic substrates have been of immense interest [81AG(E)647; 86CRV997; 87T3123; 88ACR307; 89MI1; 93T9385]. Substituted *N*-fluoropyridinium salts have become useful fluorination reagents which, regardless of the mechanism of fluorination, are often regarded as a formal source of electrophilic fluorine. Similar reagents that contain the electrophilic *N*-F function are *N*-fluoroquinuclidinium fluoride [88JCS(P1)2805], *N*-fluorosulfonamides (88TL6087), *N*-fluorosulfonimides (87JA7194), and *N*-fluoropyridin-2(1H)-one (83JOC761). This class of compounds is less expensive, more convenient, and/or safer in handling than the majority of other fluorinating agents—trifluoromethyl hypofluorite CF_3OF (80-NJC239), phenyliodonium difluoride PhIF_2 (82TL1165), trifluoroacetyl hypofluorite CF_3COOF (80JOC672), acetyl hypofluorite CH_3COOF (85-JOC4753), cesium fluorosulfate CsSO_4F (88T6505), or xenon difluoride XeF_2 (88JFC415), to name a few. The electrophilic fluorinating power (ease of fluorination) of *N*-fluoropyridinium salts increases with increasing positive charge at the ring nitrogen. Variation in the electronic effects of the ring substituents makes possible the fluorination of a wide variety of compounds differing in reactivity, while steric features arising from ring substituents or a counteranion affect selectivity of the fluorination. Solubility is an important practical factor, too. The triflate salts are quite soluble in haloalkanes, typical solvents used in fluorination, and they have been studied most extensively (90JA8563). The electrophilic power increases in the order **2b** < **1b** < **3b** < **4b** < **5b** under similar solvent conditions. The fluorination rate is decreased in acetonitrile, a polar solvent, and it is completely inhibited in tetrahydrofuran, a strongly coordinating solvent.

2. Aromatic Compounds

The most reactive pentachloropyridinium reagent (**5b**) easily fluorinated an equimolar amount of benzene in dichloromethane at reflux temperature for 2 hours to give fluorobenzene in a 48% yield but failed to react with

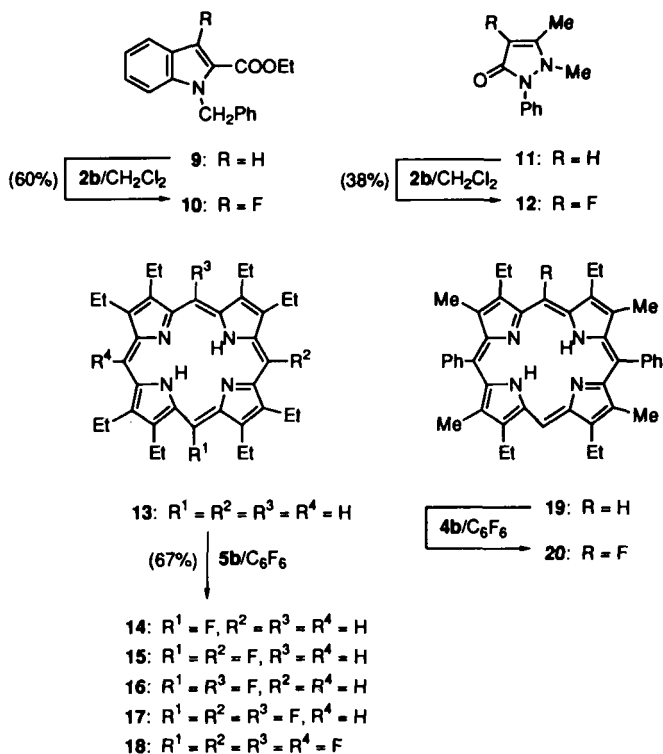
methyl benzoate, a deactivated substrate. A similar reaction of **5b** with naphthalene at room temperature furnished 1-fluoronaphthalene in a 50% yield and a trace amount of 2-fluoronaphthalene (90JA8563). Fluorination of anthracene with less reactive salts **1b** or **2b** in dichloromethane afforded a mixture of 9-fluoroanthracene and 9,10-difluoroanthracene. The use of the more reactive dichloropyridinium derivative **3b** resulted in polyfluorination of anthracene (89JOC1018). It appears that *N*-fluoropyridinium salts do not cause fluorination at the benzylic position of alkyl-substituted aromatic compounds (91JOC7347; 94UP1). The electrophilic nature of the reagents is also reflected by the exclusive ortho and para fluorination of phenols, naphthols, alkoxybenzenes, and *N*-acyl- or *N*-methoxycarbonyl-protected anilines. The ortho/para regioselectivity is superior to that observed with XeF₂ (78IJ71) or CsSO₄F (81JA1964). The reaction of inner salts (**7** or **8**) with phenols yields ortho isomers exclusively. This high regioselectivity has been explained in terms of the formation of a π -complex between the aromatic ring of the phenol and the pyridinium ring of the reagent, additionally stabilized by intermolecular hydrogen bonding between the sulfonate and hydroxy groups. The almost exclusive ortho fluorination of aniline derivatives by inner salts **7** and **8** has been rationalized in a similar fashion (90JA8563).

3. *Heterocyclic Compounds*

An indole **9** and antipyrine (**11**) were fluorinated to give the respective fluoro derivatives **10** and **12**. Attempts to fluorinate furan, pyrrole, *N*-benzylpyrrole, ethyl 2-thienylacetate, and methyl 2-thiophenecarboxylate with various salts were all unsuccessful owing to excessive tar formation (90JA8563). Porphyrins are efficiently fluorinated at meso positions, and tetrasubstituted derivatives, such as meso-tetraphenylporphyrin, are inert. The preparation of a mixture of fluorinated derivatives **14–18** from **13** and monofluorination of **19** to give **20** are instructive. Interestingly, the products **14–18** were separated into pure components by simple silica gel chromatography (92TL1069).

γ -Lactones are efficiently fluorinated by a two-step procedure (Scheme 2). The application of *N*-fluoropyridinium salts to the synthesis of nucleoside analogs is illustrated in Scheme 3. The fluorination of acid-labile substrates is often conducted in the presence of a base such as pyridine, 2-fluoropyridine, or 2,6-di-*tert*-butylpyridine (90JA8563).

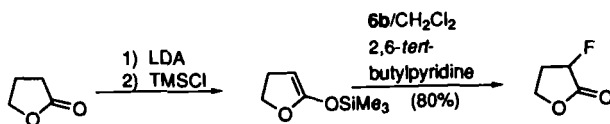
Safe conditions for a direct fluorination of substituted pyridines with molecular fluorine have been found, but the method is of little synthetic value considering the large amounts of pyridines required (87TL255). Various 2-fluoropyridines can conveniently be prepared by base-induced decomposition of *N*-fluoropyridinium salts with the unsubstituted 2/6 posi-



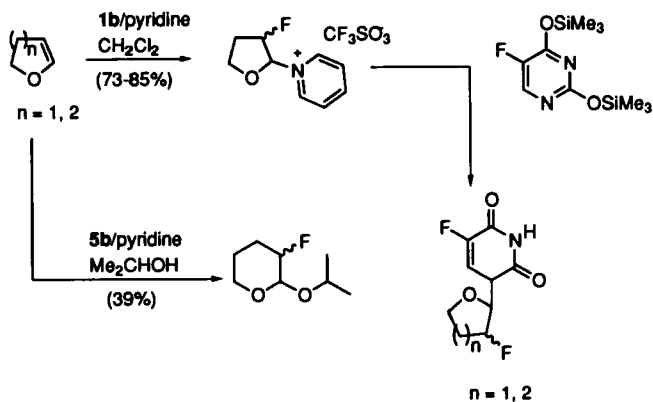
tion and BF_4^- , SbF_6^- , or PF_6^- counteranion, such as **1c–e** or **3c** (89JOC1726). The first step of this reaction apparently involves base-mediated deprotonation of the *N*-fluoropyridinium cation at the most acidic position 2 or 6 to give an intermediate carbene. This reactivity and additional examples of the fluorination are discussed in more detail in Section IV.C.2.

4. Other Derivatives

Enol alkyl ethers, enol silyl ethers, vinyl esters, and enamines undergo reactions with *N*-fluoropyridinium salts to give α -fluoroketones, as illus-

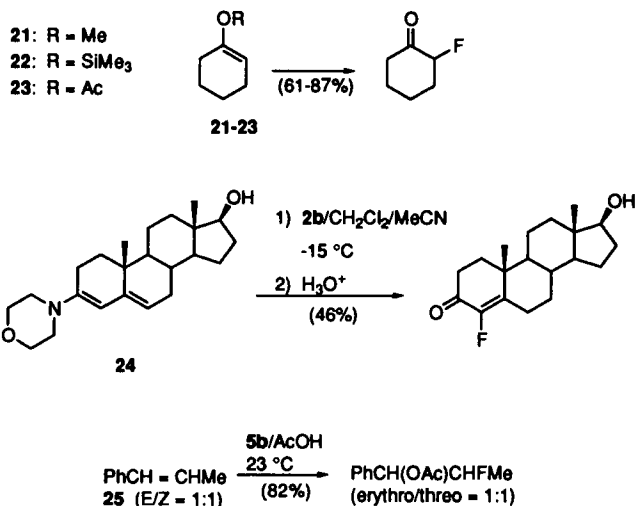


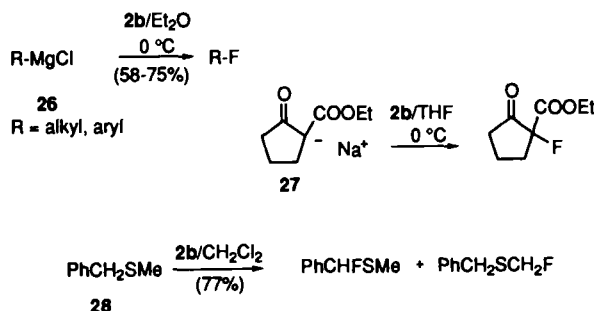
SCHEME 2



SCHEME 3

trated for the selected substrates **21–24**. The most reactive pentachloropyridinium reagent (**5b**) causes fluorination of styrene, substituted styrenes such as **25**, 1,1-disubstituted ethylenes, and trisubstituted ethylenes. This reaction often involves a nucleophilic solvent to give an addition product. Grignard reagents (**26**) and anions derived from 1,3-dicarbonyl compounds, such as **27**, are efficiently transformed into the corresponding organic fluorides. Organolithium reagents are not fluorinated by *N*-fluoropyridinium salts (86TL4465; 90JA8563; 90OS129). Sulfides such as **28** are fluorinated at the α positions. This reaction is completely suppressed in acetonitrile (86BCJ3625).

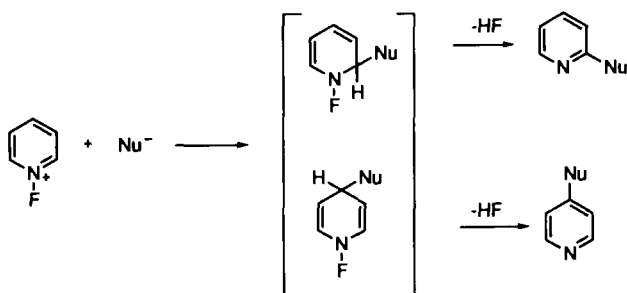




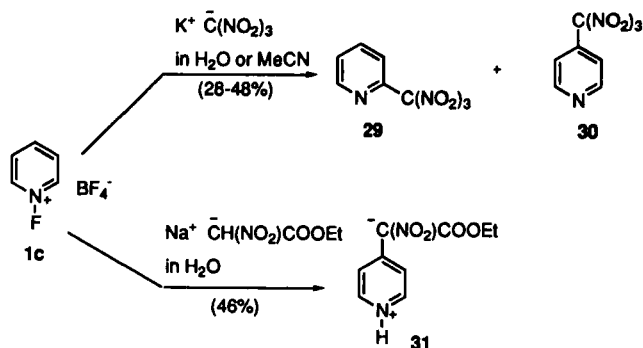
C. REACTIONS AT THE PYRIDINIUM RING SYSTEM

1. Nucleophile Additions

Highly nucleophilic species of relatively low basicity that are, at the same time, poor electron donors (78ACR413; 88ACR414) can undergo addition reactions with the *N*-fluoropyridinium cation (Scheme 4). The formation of 4-substituted pyridines, such as **30** or **31**, has been observed for the reactions of nitro group-stabilized anions. The regioselectivity of the process is influenced by the solvent. The ratio **30/29** < 1 in acetonitrile is reversed in water, and product **31** is the only isomer formed under aqueous conditions (90TL7379). A related reaction has also been described (83IZV2655). All other known reactions believed to involve the addition pathway yield 2/6-substituted pyridines exclusively. Examples are ketone **32** and esters **33–36** obtained by the reaction of the corresponding metal enolates or derivatives (90TL7379; 93JOC4476), 2-phoxypyridines (**37–41**) and 2-(phenylthio)pyridines (**42–45**) synthesized by the reaction of the corresponding metal phenoxides or benzenethiolates, and 2-hetero-



SCHEME 4

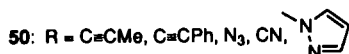
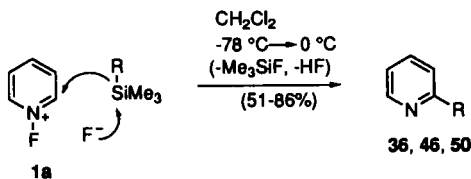


arylpiperidines (**46–49**) prepared by the reaction of sodium salts of the corresponding heterocycles with stable pyridinium reagents **1b** or **1c** (93JHC1361). The SET process has been suggested as the minor pathway in the synthesis of thioethers (**42–45**). This synthetic method is efficient, and several products, such as **40**, **45**, and **47**, could not be prepared at all by classical approaches. A novel strategy for the synthesis of 2-substituted

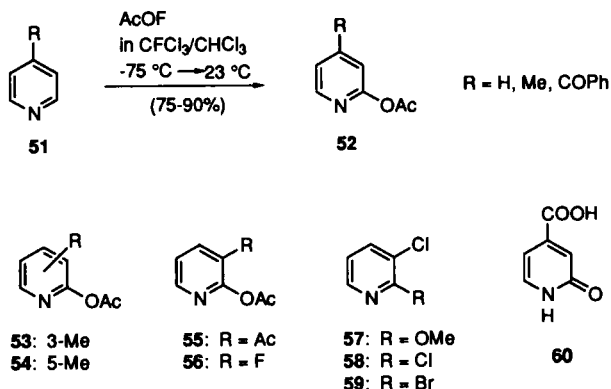
32-36			37-45			46-49	
	R	R'		Z	R		R
32	H	Me	37	O	H	46	
33	CN	OEtl	38	O	<i>o</i> -NO ₂	47	
34	COOEt	OEtl	39	O	<i>p</i> -NO ₃		
35	H	OBu- <i>t</i>	40	O	<i>o</i> -COOMe	48	
36	H	OEtl	41	O	<i>p</i> -COOMe	49	
			42	S	H		
			43	S	<i>o</i> -NO ₂		
			44	S	<i>p</i> -NO ₂		
			45	S	<i>o</i> -COOMe		

pyridines, such as **36**, **46**, and **50**, involves the reaction of trimethylsilyl derivatives with N -fluoropyridinium fluoride (**1a**) generated in situ from pyridine and molecular fluorine (93JOC4476). The reactions of isomeric O - and C -trimethylsilyl reagents yield a C -substituted product exclusively because the same carbanion is generated in both cases by the interaction of fluoride with the silicon derivatives.

The efficient synthesis of 2-acetoxypyridines, such as **52**, by the reaction of the corresponding pyridines (**51**) with acetyl hypofluorite is also believed to involve the initial formation of N -fluoropyridinium cation followed by



its addition reaction with acetate anion (87JA3789; 89H249). A mixture of two isomers (**53** and **54**) was obtained from 3-methylpyridine under similar conditions. On the other hand, the reaction of AcOF with pyridines containing an electron-withdrawing substituent at the 3 position is highly regioselective and yields a 2-acetoxy derivative, such as **55** or **56**. The 2-regioselectivity can be explained in terms of a greater electron deficiency at position 2 than at position 6, as induced by the electron-withdrawing group at the 3 position of the *N*-fluoropyridinium cation. Alcohol used as a solvent can apparently compete with acetate ion for the addition reaction with the intermediate *N*-fluoropyridinium cation (88JOC1123; 91JOC6298). For example, ether **57** was obtained regioselectively in 75% yield upon treatment of a methanolic solution of 3-chloropyridine with a standard solution of AcOF in CFC₃. A rather unusual transfer of a halogen from dichloromethane or dibromomethane used as a solvent to the pyri-



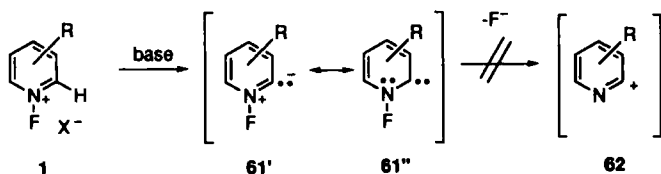
dinium cation takes place to give the corresponding 2-halogenopyridine, such as **58** or **59**, in an excellent yield. Rozen and Hebel have studied this process extensively and concluded that it involves the addition of the nucleophilic Cl^{δ-} or Br^{δ-} originating from the solvent (88JOC1123; 91JOC6298). An alternative mechanistic pathway would involve proton

abstraction from position 2 of the cation in which the acetate ion acts as a base. This pathway is discussed in more detail in Section IV.C.2. All attempts to introduce iodine by employing iodoalkanes were unsuccessful because these solvents were oxidized by AcOF to produce iodine. The successful activation of a pyridine ring toward nucleophilic solvents has been achieved by using CsSO_4F instead of AcOF (90TL775). A mechanistically related synthesis of 2(1H)-pyridones, such as **60**, by activation of the corresponding pyridine derivative with molecular fluorine in water has been reported (88TL4389).

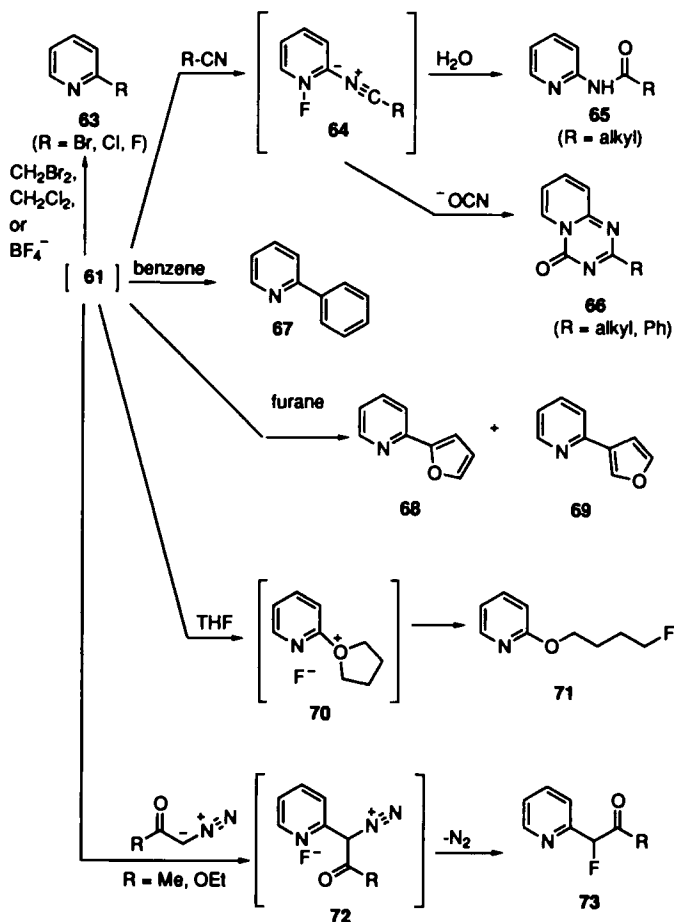
2. Base-Mediated Transformations

Many reactions of *N*-fluoropyridinium salts containing an unsubstituted position 2 and/or 6, and as **1** and **3**, have been explained in terms of the base-mediated generation of the intermediate product **61** (Scheme 5). Owing to the electrophilic nature of the presumed intermediate product, the carbene-contributing structure (**61''**) is favored over the ylid (**61'**) by theoretical calculations (94TL207; 94UP2). These computations have also strongly suggested that the loss of fluoride anion from **61** to give an intermediate cation (**62**) is highly unlikely (72CB8; 94UP2).

Reactions of *N*-fluoropyridinium salts with the suggested intermediacy of **61** are illustrated in Scheme 6. Examples include syntheses of 2-halogenopyridines (**63**), amides (**65**), 2-phenylpyridine (**67**), furylpyridines (**68** and **69**), and an ether **71** in the presence of triethylamine (87TL2705; 89JOC1726). Bases as weak as fluoride ion, water, or cyanate ion apparently can deprotonate the *N*-fluoropyridinium cation and then act as nucleophiles under the conditions of an improved synthesis of amides (**65**) (94SC2387) and a novel preparation of pyridotriazines (**66**) (94TL207). These transformations may involve the intermediacy of a nitrilium ylid (**64**) generated by the reaction of **61** with carbonitrile. Finally, it has been postulated that diazocarbonyl compounds are both bases and nucleophiles in the novel synthesis of 2-substituted pyridines **73** [94H(38)259]. A fascinating feature in the suggested mechanistic pathways **70** \rightarrow **71** and **72** \rightarrow **73** is the transfer of fluoride anion derived from the electrophilic *N*-fluoropyridinium cation.



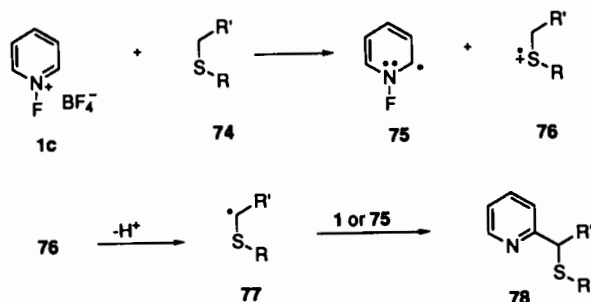
SCHEME 5



SCHEME 6

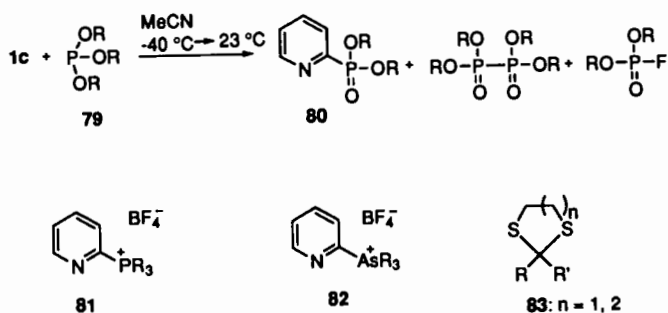
3. Homolytic Reactions

Good electron donors such as sulfides, phosphines, or arsines can react with *N*-fluoropyridinium cation by a single-electron transfer (SET) pathway. This conclusion was reached after finding products known to be derived from free-radical processes. For example, it is believed that the SET process is operative in the reaction of sulfides (74) to give pyridyl-substituted sulfides (78) through the intermediary of a radical 75 and a radical cation 76 (Scheme 7). In addition to 78 this reaction produces a dimer of a radical 77 derived from the radical cation (76) and a number of other products known to be formed from 76 or 77 (93JHC329). The



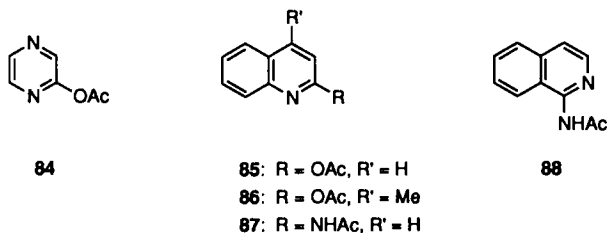
SCHEME 7

formation of **78** is regioselective because nucleophilic alkyl radicals, such as **77**, selectively attack the most electrophilic position 2 of the pyridine ring or pyridinium cation (85MI1). The SET process is apparently operative in the reaction of trialkoxyphosphines (**79**) with an *N*-fluoropyridinium salt (**1c**) to give a phosphonate ester (**80**) and in high-yield syntheses of phosphonium salts (**81**) and arsonium salts (**82**) from phosphines and arsines, respectively (91MI1). A novel, efficient hydrolysis of dithioacetals (**83**) by a salt **2b** in the presence of water to give the corresponding parent carbonyl compounds may also involve the SET process (93T2151).



V. Future Perspectives

It has been shown that, apart from their more obvious function as fluorinating agents, elemental fluorine and fluorine-transfer reagents can be used for an array of processes leading eventually to difficult-to-obtain, fluorine-free organic compounds. Stable *N*-fluoropyridinium salts and derivatives generated in situ can successfully be applied in the regioselective synthesis of 2-substituted pyridines. Nothing better describes the rapidly



growing role of fluorine in the chemistry of pyridines than the statement that fluorine is "a legitimate tool" not only to perform fluorination reactions, but also to accomplish more general organic synthesis (91JOC6298).

Additional mechanistic studies are needed in order to understand and control better the high reactivity of the *N*-fluoropyridinium cation. Our knowledge of factors that affect the formation of this cation is also far from complete. The suggestion that there is a limit in basicity of the pyridine nitrogen, below which the *N*-fluoropyridinium cation is not formed, certainly deserves systematic quantitative studies (89H249; 94UP3). A better understanding of the interaction of elemental fluorine with pyridines would also facilitate work on the extension of this type of chemistry to other nitrogen heterocycles. The few successful examples described to date are high-yield syntheses of acetates **84–86** (89H249) and acetamides **87, 88** (94SC2387) by the reactions of the corresponding parent azaaromatic substrates that presumably involve transient *N*-fluoroazinium cations.

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New Developments in the Chemistry of Pyrans

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I. Introduction	20
II. Nomenclature	20
III. Synthesis from Acyclic Precursors	20
A. From 1,5-Dicarbonyl and Analogous Precursors	21
B. From 1,3-Dicarbonyl and Related C-Acids	24
C. From Acetylenes	40
D. From Dienals and Dienones	45
E. From Other Acyclic Compounds	48
IV. Synthesis from Cyclic Precursors	51
A. From Pyrylium Salts	51
B. From Dihydropyrans	62
C. From Pyrones and Dihydropyrones	65
D. From Other Pyrans	66
E. From Other Heterocycles	66
V. Reactions	68
A. Aromatization and Oxidation	68
B. Reduction	75
C. Isomerization	77
D. Ring-Opening Reactions	84
E. Substitution Reactions	88
F. Conversion to Carbocyclic Systems	92
G. Conversion to Other Heterocycles	94
H. Functional-Group Transformations	100
I. Cycloaddition Reactions	107
J. Formation of Metallic Complexes	109
K. Other Transformations	110
VI. Physical Properties and Theoretical Chemistry	111
A. Molecular Energy and Electronic Structure	111
B. Electronic Spectra	113
C. Nuclear Magnetic Resonance	113
D. Infrared Spectra	113
E. X-Ray Crystallography and Molecular Structure	115
F. Other Spectroscopic Techniques	117
G. Miscellaneous	120
VII. Other Properties	120
References	121

I. Introduction

Pyran chemistry was reviewed by one of the authors in 1983 [83AHC(34)145] and in part by others [80H337; 82QP; 83KGS1011; 85KGS291]. Many interesting properties of pyrans have been discussed in two chapters of *Comprehensive Heterocyclic Chemistry* [84CHC(3)573; pyrans 84CHC(3)737]. Some special topics regarding pyran derivatives are subjects of several articles (82AHC(S)140; 82UK817; 84KGS1011; 85UK1971; 86OPP227). This review is an attempt to discuss the literature of the last decade as covered by *Chemical Abstracts* up to the middle of 1993. Only isolable, quantum chemically calculated or spectroscopically identifiable pyrans without exocyclic double bonds are considered. Also excluded are all benzo derivatives such as chromenes and xanthenes. The chemistry of corresponding thia, seleno, and telluro analogs (heteropyrans) has been reviewed in a recent volume of *Advances in Heterocyclic Chemistry* [94AHC(59)179].

II. Nomenclature

The term *pyran structure* used here applies to a six-membered ring possessing one oxygen singly bonded in a cyclic system of two double bonds and one tetrahedral atomic center. According to the current terminology the original names, *2H*-pyran and *4H*-pyran, are still more commonly used than the systematically proposed 2- and 4-oxines [84CHC(1)7; 84CHC(3)573]. The numbering of the heterocyclic rings is shown in formulas **1** and **2**.

Of the parent unsubstituted compounds only the *4H*-isomer **2** has been repeatedly prepared (85CB5018). Attempts to prepare the *2H*-isomer in a pure state were unsuccessful [85DIS(B)840] although it was apparently trapped as a ligand in molybdenum coordination salts (90JA9660).

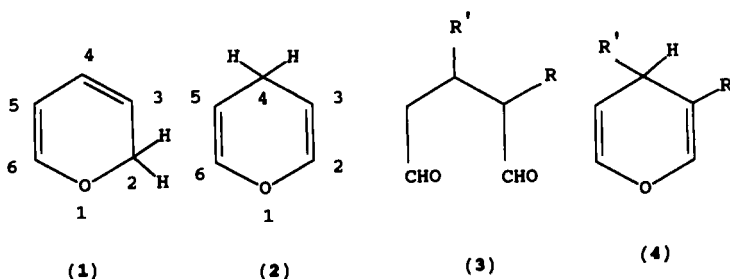
III. Synthesis from Acyclic Precursors

In this section the expressions “acyclic” or “cyclic” precursors are used to indicate whether a pyran-ring closure does or does not occur, respectively, during synthesis. No importance is attributed to the fact that reactants may already contain a ring.

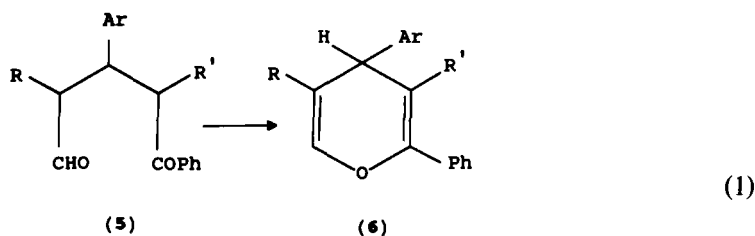
A. FROM 1,5-DICARBONYL AND ANALOGOUS PRECURSORS

This approach to 4*H*-pyrans consisting in cyclodehydration of the 1,5-dicarbonyl derivatives has been used in many examples.

1,5-Dialdehydes **3** were cyclodehydrated to methyl-4*H*-pyrans **4** ($R = \text{Me}$, $R' = \text{H}$; $R = \text{H}$, $R' = \text{Me}$), and the same method was successfully used for the preparation of 2,5-dideuterated **2** from 1,4,4-trideuterio-glutaric dialdehyde (86OMS459).

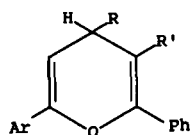


1,5-Ketoaldehydes **5a** were easily transformed to 4*H*-pyrans **6a** according to Eq. (1) (89AP617). A number of substituted 1,5-diketones were successfully converted to corresponding heterocycles **7** (92KGS320), **8a** (87CP623; 89CCC1854; 92CCC2383), **8b** [89CCC1854; 91JCS(P2)2061], **8c,d**, **9** [87CP623; 89CCC1854; 92JCS(P2)1301], **10** ($\text{Ar} = \text{Ph}$, 2-MeC₆H₄; $R = \text{H}$, Me; $R' = \text{H}$, Me, Pr, Ph, subst. Ph; $n = 0, 1$), and **11** [$R = \text{H}$, Me, Pr, Ph, subst. Ph; $X = \text{H}_2$; $n = 0, 1$ (92KGS320); and $R = \text{H}$; $X = \text{PhCH}$, 4-MeOC₆H₄CH, (2-furyl)CH; $n = 1$ (83ZOR2516)] by heating with ethanolic HCl (83ZOR2516), PPA or 85% H₃PO₄ (89AP617), P₄O₁₀ in xylene [87CP623; 89CZP261434; 92JCS(P2)1301], *p*-TsOH in toluene (89CCC1854), I₂ in toluene (92CCC2383), or with an Ac₂O–BF₃–Et₂O mixture (92KGS320).

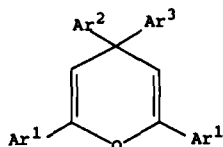


(a) $R = i\text{-Pr}$, Ph ; $R' = \text{H}$; $\text{Ar} = \text{Ph}$, 4-NO₂C₆H₄

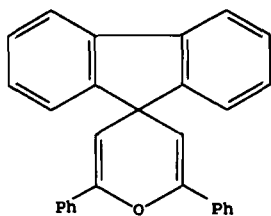
(b) $R = i\text{-Pr}$; $R' = \text{CO}_2\text{Et}$; $\text{Ar} = \text{Ph}$, 3-NO₂C₆H₄



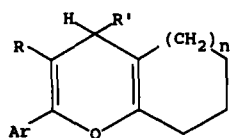
(7)



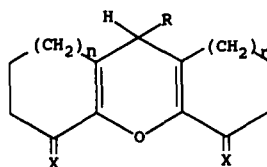
(8)



(9)

(a) $\text{Ar}^1 = \text{Ar}^2 = \text{Ar}^3 = \text{Ph}$ (b) $\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$; $\text{Ar}^3 = 4\text{-XC}_6\text{H}_4$ (X: Br, Cl, Me)(c) $\text{Ar}^1 = 4\text{-XC}_6\text{H}_4$ (X: t-Bu, Br, F, Me, MeO); $\text{Ar}^2 = \text{Ar}^3 = \text{Ph}$ (d) $\text{Ar}^1 = \text{Ph}$; $\text{Ar}^2 = \text{Ar}^3 = 4\text{-XC}_6\text{H}_4$ (X: Br, t-Bu, F)

(10)

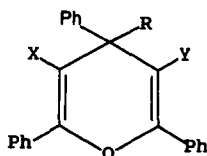


(11)

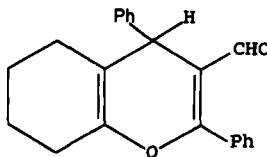
R and X, see text

On the other hand, when halogenides, PCl_5 , or DMF-POCl_3 mixtures were used as the cyclodehydrating agents, the initially arising 4*H*-pyrans underwent electrophilic 3,5-halogenations or 3- and 3,5-formylations, affording halogeno derivatives **12a** (R = Ph; X = Y = Cl, Br) or aldehydes **12b** (R = Ph, X = H, Y = CHO) (92CCC2383), **12c** (R = H, X = Y = CHO), and **13** (91TL3235).

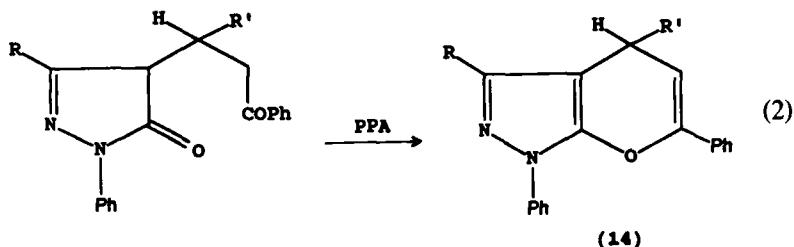
One of the oxo groups in a 1,5-dioxo starting compound may be a part of the heterocyclic ring as found (82KGS317) for example in the synthesis of pyrazolo pyrans **14** (R = Me, Ph; R' = Ph, 3- $\text{O}_2\text{NC}_6\text{H}_4$) according to Eq. (2).



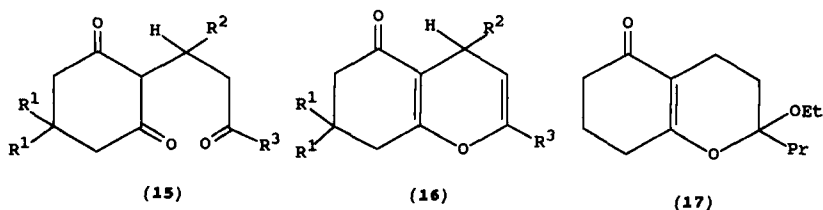
(12a-c)



(13)



Aldehydo-keto esters **5b** also were found capable of the heterocyclization with *p*-TsOH on heating in benzene, yielding **6b** without the participation of the ethoxycarbonyl group (89AP617). Triketones of type **15** were easily converted to the expected 4*H*-pyran **16a** in a *p*-TsOH-EtOH-C₆H₆ solution and subsequent distillation (84BCJ3351), or to pyrans **16b** and **16c** by treatment with BF₃-Et₂O-Ac₂O-AcOH mixtures (82ZOR2184; 85KGS915). The intermediate acetal **17** was quantitatively trapped in the case of **16a** (84BCJ3351).

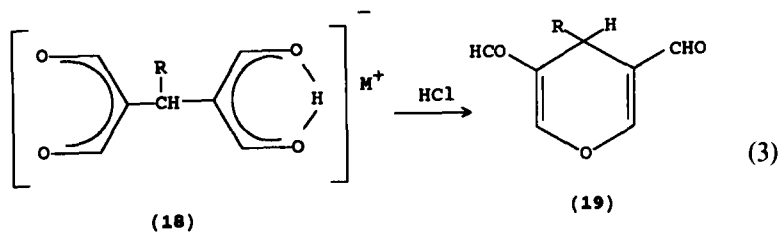


(a) R¹ = R² = H; R³ = Pr

(b) R¹ = H; R² = Ph, 4-MeOC₆H₄; R³ = 4-MeOC₆H₄, Ph

(c) R¹ = Me; R² = Ph, 4-MeOC₆H₄; R³ = Ph

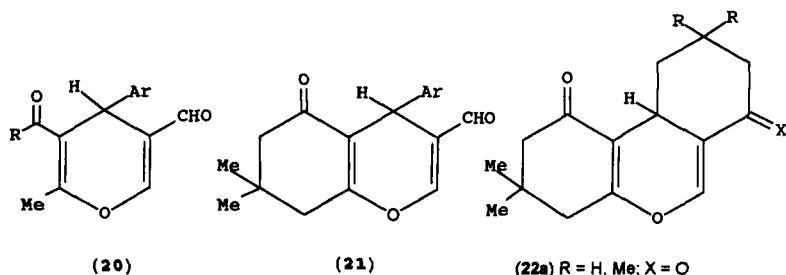
4-Substituted 4*H*-pyran-3,5-dicarbaldehydes **19** were obtained after acidification of appropriate tetraaldehyde alkali salts **18** (85LA1987; 90TL4077; 93T1237) in agreement with Eq. (3). A similar approach starting, however, from free dioxo-dialdehyde precursors gave 4*H*-pyrans **20** and **21** by heating with *p*-TsOH in benzene (87CCC2687). Analogous tricyclic pyrans **22** (R = H, Me) were similarly prepared from appropriate tetraketones using *p*-TsOH or P₄O₁₀ as cyclodehydrating agents (83ZOR2027). When the keto group in the precursors is changed to a cyano group, the corresponding 2-amino-4*H*-pyrans **23a** (87CCC2687) and **23b** (89APR201) are formed essentially spontaneously. Some other **23**-like products were prepared via the corresponding open-chain intermediates by procedures (88ZOR460; 89APR201) discussed in Section III.B.2b.



$M = \text{Na}, R = \text{Me}, \text{CH}_2\text{CHO}, \text{CH}_2\text{CHOMe}, n\text{-C}_3\text{H}_7, n\text{-C}_5\text{H}_{11};$

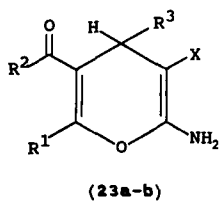
$M = \text{K}; R = \text{Ph}$

Keto-nitriles also are candidates as precursors for the preparation of 6-amino-2H-pyrans, as shown in Scheme 1 (87KGS653).



$R = \text{Me}, \text{OEt}; \text{Ar} = 4\text{-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3\text{-thienyl}$

(22b) $R = \text{H}; X = \text{H}_2$



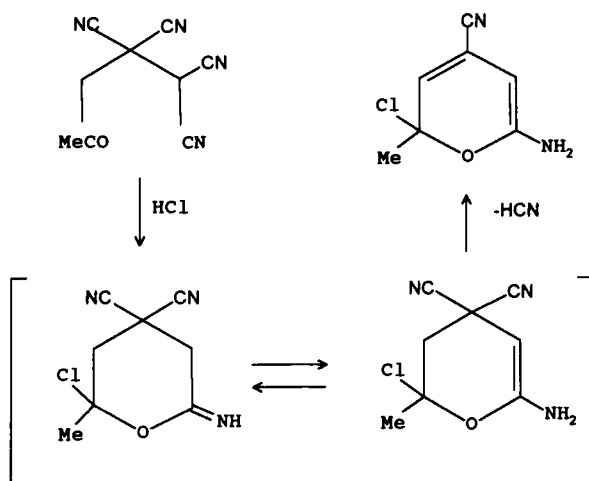
(23a) $R^1 = R^2 = \text{H}; R^3 = 4\text{-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3\text{-thienyl}, \text{Cl}_2\text{C}=\text{CH}-\text{CH}=\text{CH}; X = \text{CN}, \text{COOMe}$

(23b) $R^1 = \text{Me}; R^2 = \text{PhNH}; R^3 = \text{Ph}, 4\text{-YC}_6\text{H}_4$

$Y: \text{Cl}, \text{Me}, \text{MeO}, \text{NO}_2, \text{CN}$

B. FROM 1,3-DICARBONYL AND RELATED C-ACIDS

This commonly used approach is demonstrated considering the typical products, 2H-pyrans or 4H-pyrans. Typical substituent patterns in the synthesized molecules are also indicated.

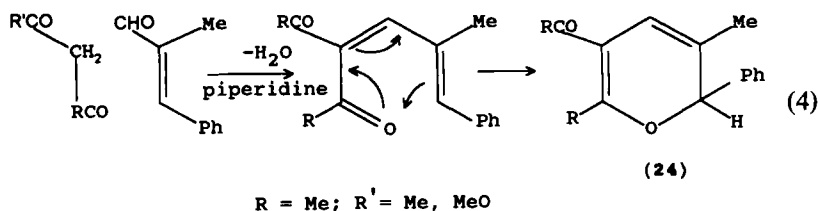


SCHEME 1

1. Preparation of 2H-Pyrans

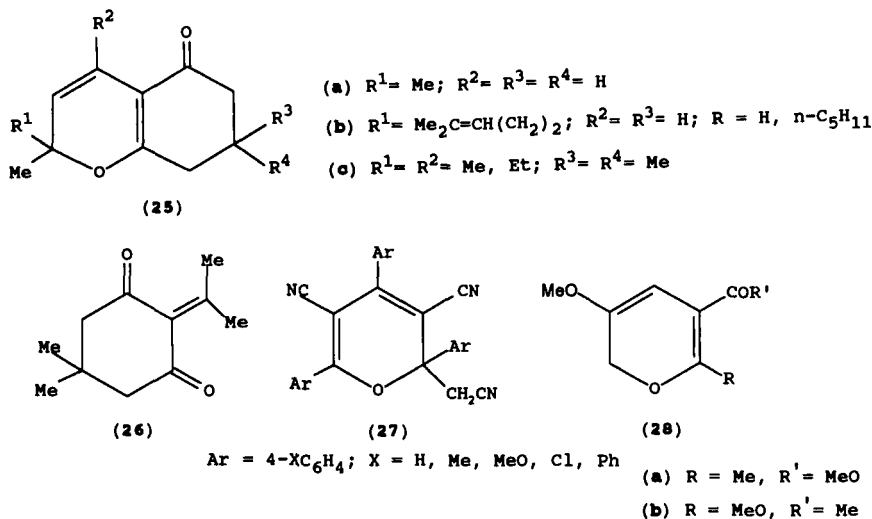
The formation of the title heterocycles is probable in some cases when an unstable dienone molecular substructure (see Section V.C.1) is created from the starting reactants.

a. *From α,β -Unsaturated Aldehydes.* The precursors with 1,3-dicarbonyl partners under the conditions of the Knoevenagel condensation usually afford 2H-pyrans instead of expected dienones, as shown in Eq. (4) for isolated products **24** (88IZV1815). Bicyclic 2H-pyrans **25a** and **25b** were obtained analogously from $\text{Me}_2\text{C}=\text{CHCHO}$ (84JHC913; 87JOC1972) or citral (82S683) and the corresponding cyclohexane-1,3-diones with MgSO_4 -pyridine or ethane-1,2-diammonium acetate condensing reagents.

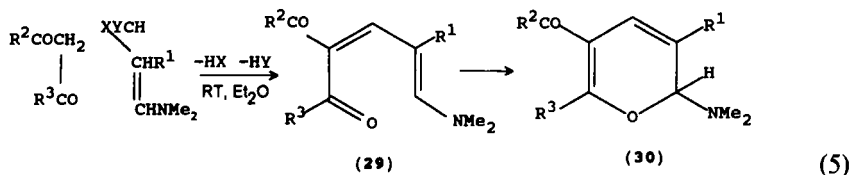


b. *From Ketones and Keto Acid Derivatives.* 2*H*-Pyrans **25c** were found to be readily formed by treatment of ketones RCOMe with dimedone and Et₃N. The transformations proceed via 2-alkylidene cyclohexane-1,3-diones, as proved for the case R¹ = R² = Me by the separate conversions of Me₂CO + dimedone → **26** and **26** → **25c** [89IJC(B)81]. The known three-component condensation of ketonitriles ArCOCH₂CN to 2*H*-pyran tricyano derivatives **27** has also been patented (84CZP213692).

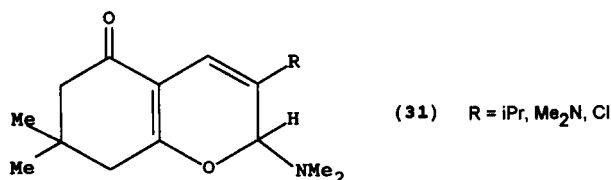
Formula **28b** has been proposed for two by-products obtained after the reaction of methyl 3-acetyl-4-bromo-pent-2-enoate with a MeONa–MeOH mixture at 0°C (83BSB371).



c. *From N,N-Dimethylenamino Precursors.* 2-Dimethylamino-2*H*-pyrans are readily obtainable from 1,3-dicarbonyl compounds and the corresponding β-dimethylamino-α,β-unsaturated aldehyde derivatives when the products are thermodynamically more stable than their open-form valence isomers. Typical precursors in the synthesis via open-form intermediates **29** to 2*H*-pyrans **30a** (85IZV1075) and **30b–d** (88KGS1325) are evident from Eq. (5). The same procedure was explored for the preparation of oligocyclic 2*H*-pyrans **31** (85IZV1075; 88KGS1325). In other cases acyclic valence isomers **29** or mixtures of **29** and **30** were obtained (85IZV1075; 86IZV1596; 87IZV821, 88KGS1325).

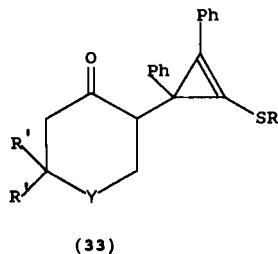
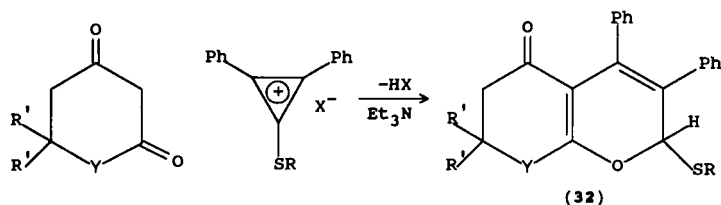


- $X, Y = \text{Me}_2\text{N}, \text{Me}_2\text{N}; \text{Me}_2\text{N}, \text{MeO}; \text{MeO}, \text{MeO}$ (a) $\text{R}^1 = \text{Cl}; \text{R}^2 = \text{EtO}; \text{R}^3 = \text{Me}, \text{H}$
 (b) $\text{R}^1 = i\text{-Pr}, \text{Me}_2\text{N}; \text{R}^2 = \text{R}^3 = \text{Me}$
 (c) $\text{R}^1 = i\text{-Pr}, \text{Me}_2\text{N}; \text{R}^2 = \text{MeO}; \text{R}^3 = \text{Me}$
 (d) $\text{R}^1 = i\text{-Pr}, \text{Me}_2\text{N}; \text{R}^2 = \text{EtO}; \text{R}^3 = \text{Ph}$



A similar procedure using **29**-like intermediates was patented for the preparation of 2-methoxy-3,6-diaryl-2H-pyrans (86JPP6124571).

d. *From Alkylthiocyclopropenium Salts.* A quite new approach to 2-alkylthio-2H-pyrans **32** has been found in the reaction of the title precursors with carbocyclic or heterocyclic 1,3-dienones and Et_3N (83H1013; 84BCJ734). The formation of **32** is believed to proceed via intermediates **33**. Oligocyclic 2H-pyrans **34** and **35** were prepared in the same way (84BCJ734).

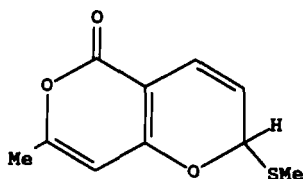


$\text{Y} = (\text{CH}_2)_n$

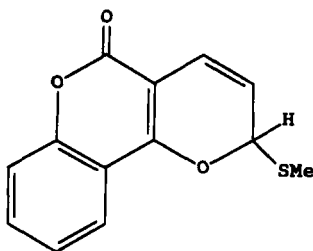
$n = 0; \text{R} = \text{Me}; \text{R}' = \text{H}; \text{X} = \text{Br}$

$n = 1; \text{R} = \text{Me}, \text{Et}, \text{PhCH}_2; \text{R}' = \text{H}, \text{Me}; \text{X} = \text{Br}, \text{I}$

$n = 2; \text{R} = \text{Me}; \text{R}' = \text{H}; \text{X} = \text{Br}$

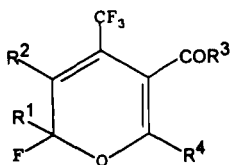


(34)



(35)

e. *From Perfluoroalkenes.* The reactions of the title electrophilic precursors with sodium 1,3-dicarbonyl enolates exhibit generally low selectivities, usually yielding 14–30% fluorinated 2*H*-pyrans **36a–d** as well as other products. Thus, the following transformations were performed: $\text{CF}_3\text{CF}=\text{CFCF}_3 + \text{CH}_2(\text{CO}_2\text{Et}) \rightarrow \mathbf{36c}$, $\text{C}_2\text{F}_5\text{C}(\text{CF}_3)=\text{CFCF}_3 + \text{AcCHCO}_2\text{Et} \rightarrow \mathbf{36d}$ [83JCS(P1)1239], and $\text{F}_2\text{C}=\text{C}(\text{CF}_3)-\text{C}(\text{CF}_3)=\text{CF}_2 + \text{AcCH}_2\text{CO}_2\text{Et}$ or $\text{Ac}_2\text{CH}_2 \rightarrow \mathbf{36a}$ or **36b**, respectively. Sodium hydride in tetraglyme was used as a reagent, and a reaction mechanism has been discussed [83JCS(P1)2451]. Contrary to these findings, analogous 4*H*-pyran structures have been proposed for products of the reaction of $\text{C}_2\text{F}_5(\text{CF}_3)\text{C}=\text{C}(\text{CF}_3)\text{C}_2\text{F}_5$ with sodium salts of Ac_2CH_2 , $\text{AcCH}_2\text{CO}_2\text{Et}$, and $\text{CH}_2(\text{CO}_2\text{Et})_2$ [83JCS(P1)1235]. Hence, the earlier conclusions should be corrected.

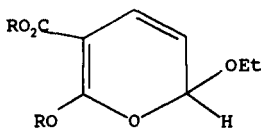


(36a) $\text{R}^1 = \text{F}$, $\text{R}^2 = \text{C}(\text{CF}_3)=\text{CF}_2$, $\text{R}^3 = \text{EtO}$, $\text{R}^4 = \text{Me}$

(36b) $\text{R}^1 = \text{F}$, $\text{R}^2 = \text{C}(\text{CF}_3)=\text{CF}_2$, $\text{R}^3 = \text{R}^4 = \text{Me}$

(36c) $\text{R}^1 = \text{R}^2 = \text{F}$, $\text{R}^3 = \text{R}^4 = \text{EtO}$

(36d) $\text{R}^1 = \text{R}^2 = \text{CF}_3$, $\text{R}^3 = \text{EtO}$, $\text{R}^4 = \text{Me}$



(37)

$\text{R} = \text{Me}, \text{Et}$

f. *From Other Precursors.* Attempts to use malonaldehyde bis(diethyl acetal) with dialkyl malonates as the precursors resulted in equilibrium mixtures of 2,6-dialkoxy-2*H*-pyrans **37** with their open valence isomers (90IZV2561). 2*H*-Pyran-5-sulfone **38** could be prepared up to 67% yield by a base-catalyzed decarboxylative transformation from methyl 2-

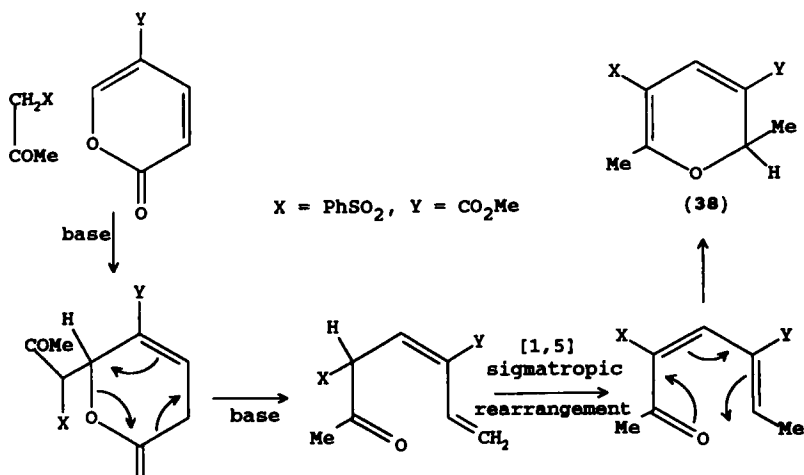
pyrone-5-carboxylate and C-acidic $\text{PhSO}_2\text{CH}_2\text{COMe}$. This synthesis probably proceeds via cyclic transition states (Scheme 2) optimized with respect to base and solvent effects using an automatic apparatus (84JA7143).

An unusual approach to 2,2-dimethyl-5-methoxycarbonyl-2*H*-pyran was found in the reaction of dimethylaminomethylene malonaldehyde with an appropriate Grignard reagent (88TL2861), as shown in Scheme 3.

2. Preparation of 4*H*-Pyrans

This approach, which resembles the well-known Hantzsch synthesis of π -isoelectronic 1,4-dihydropyridines usually catalyzed with organic bases (piperidine), has been widely used in the last decade, especially because of pharmaceutical and agrochemical interest in the resulting 4*H*-pyran derivatives. Two-component procedures starting from α,β -unsaturated carbonyl compounds or nitriles have been shown to be more effective than three-component procedures using simple aldehydes or ketones.

a. Two-Component Versions from α,β -Unsaturated Carbonyl Compounds. This process usually consists in a base-catalyzed Michael addition of a given C-acid to the $\text{C}=\text{C}-\text{C}=\text{O}$ system, after which cyclocondensation or cycloaddition stages proceed depending on the character of the second component. The carbonyl components give rise to cyclocondensations to 4*H*-pyrans according to Eq. (6) as summarized in Table I, while nitriles offer a variety of 2(6)amino-4*H*-pyrans by cycloaddition [Eq. (7)], as shown in Table II.



SCHEME 2

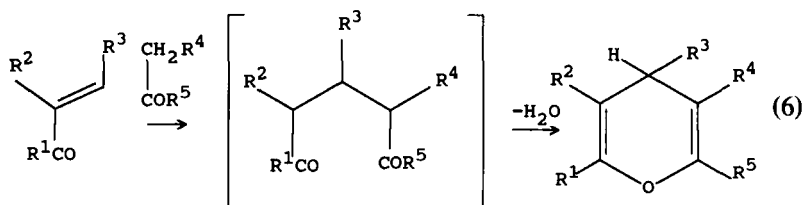
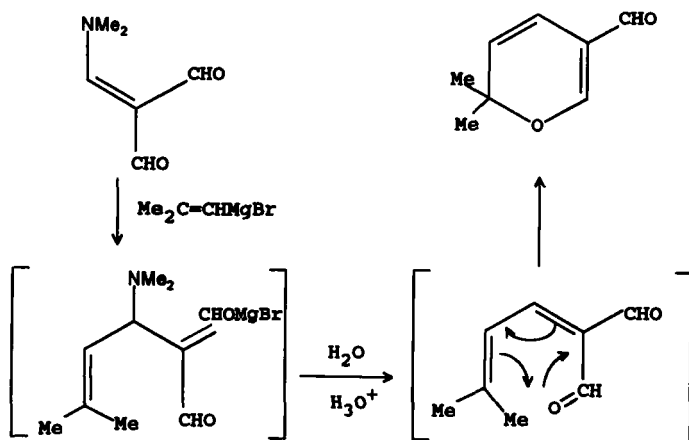


TABLE I
4H-PYRANS PREPARED ACCORDING TO EQ.(6)

R ¹	R ²	R ³	R ⁴	R ⁵	References
Me	CN	Ph	CN	Me	84H1989 ^a
Ph	H	Ph	COCH ₂ C(Me) ₂ CH ₂		82IJC(B)470
Ph	Ph	CO ₂ H	Ph	Ph	83RRC623 ^b
Ph	CN	Ph	MeCO	Me	91JPR345
Ph	CN	Ph	PhNHCO	PhNHCOCH ₂	86JHC1203
Ph	CN	4-MeOC ₆ H ₄	MeCO	Me	86H935
Ph	CN	4-MeOC ₆ H ₄	PhNHCO	PhNHCOCH ₂	86JHC1203
2-HO—4-MeOC ₆ H ₃	H	Ph	MeCO	Me	83H2369 ^c
2-HO—4-MeOC ₆ H ₃	H	4-MeOC ₆ H ₄	MeCO	Me	83H2369 ^c
2-HO—4,6-(MeO) ₂ C ₆ H ₂	H	Ph	MeCO	Me	83H2369 ^c

^a Starting α,β -unsaturated component generated *in situ*.

^b See also 83EJC189.

^c Products are components of more complex reaction mixtures.

TABLE II
4*H*-PYRANS PREPARED ACCORDING TO EQ.(7)

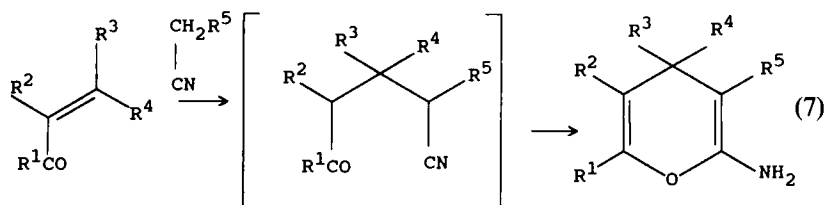
R ¹	R ²	R ³	R ⁴	R ⁵	References
H	CHO	4-ClC ₆ H ₄	H	CO ₂ Me, CN	87CCC2687
H	CHO	4-MeOC ₆ H ₄	H	CN	87CCC2687
H	CHO	3-thienyl	H	CO ₂ Me, CN	87CCC2687
H	CHO	Cl ₂ C=CH—CH=CH	H	CN	87CCC2687
H ^a	CN	Ph, 4-MeC ₆ H ₄	H	CN	85JCS(P1)2581
Me	CN	<i>s</i> Bu, <i>i</i> Pr	H	CN	85JCS(P1)2581
Me	CN	Ph	H	CN	85JCS(P1)2581
Me	CN	4-XC ₆ H ₄ ^b	H	CN	85JCS(P1)2581
Me	MeCO	2-furyl	H	CN	90CCC718
Me	MeCO	5-X-2-furyl ^c	H	CN	90CCC718
Me	MeCO	Ph	H	CN	86OPP227; 88T5861; 92T1581
Me	MeCO	4-XC ₆ H ₄ ^d	H	CN	88T5861
Me	EtO ₂ C	Ph	H	CN	84H1; 87H2811
Me	EtO ₂ C	XC ₆ H ₄ ^e	H	CN	84H1, 87H2811
Me	RO ₂ C ^f	3-O ₂ NC ₆ H ₄	H	CO ₂ Et	82GEP3208628
Me	RNHCO	Ph	H	CN	93LA801
Ph	H	Ph, PhCH=CH	H	CN	88TL2703
Ph	H	1-naphthyl	H	CN	88TL2703
Ph	PhCO	Ph	H	CN	86OPP227
Ph	PhCO	4-XC ₆ H ₄ ^g	H	CN	86OPP227
Ph	CN	Me	Me	CN	84H1
Ph	CN	Me	Et	CN	84H1

(continues)

TABLE II (continued)

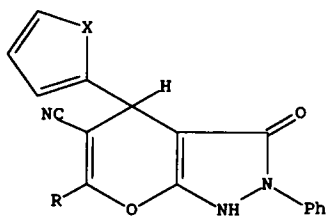
R ¹	R ²	R ³	R ⁴	R ⁵	References
Ph	CN	<i>s</i> Bu, Et ₂ CH, <i>i</i> Pr	H	CN	85JCS(P1)2581
Ph	CN	Ph	H	CN	82M53; 82RPQ133
Ph	CN	Ph	H	CO ₂ Et	82M53; 90LJC(B)1020
Ph	CN	Ph	NCCH ₂	CO ₂ Et, CN	85H1999
Ph	CN	2-furyl	H	CN	83LA1468
Ph	CN	2-thienyl	H	CN	83LA1468
Ph	CN	Het ^h	H	CN	87RRA281
Ph	EtO ₂ C	Het ^h	H	CN	87RRA281
PhCH=CH	CN	Ph	H	CN	85H2983
					86M247
4-PhC ₆ H ₄	CN	Ph	H	CN, CO ₂ Me	83CCC3123
XC ₆ H ₄ ⁱ	XC ₆ H ₄ ⁱ	4-YC ₆ H ₄ ^j	H	CN	83H803
—C(=CHPh)(CH ₂) ₂ —		Ph	H	CN	88TL2703
—C(=CHPh)(CH ₂) ₃ —		Ph	H	CN	88TL2703
—(O)C ₆ H ₄ O(S)CH ₂ —		Ph	H	CN	88TL2703
—N(Ph)CSN(Ph)—		Ph, 4-O ₂ NC ₆ H ₄	H	CN	82S502

^a α,β -Unsaturated component generated *in situ*.^b X = Me, MeO.^c X = Me, PhO, MeO₂C, and PhS.^d X = Me, MeO.^e X = 4-Cl, 4-CN, 4-Me, 4-MeO, 3-O₂N, 4-O₂N.^f R = *n*C₁₀H₂₁.^g X = Cl, Me, NO₂.^h Het = furyl, pyridyl, and pyrrolyl.ⁱ X = H, 4-MeO.^j X = H, Cl, Me, MeO.

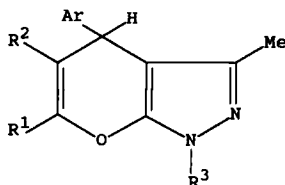


Sometimes the intermediate Michael adducts were trapped [83ZOR2609; 84H1989; 91JPR(A)345], detected (87CCC2687), or isolated as final products (83H803; 84H1). Several reported 4*H*-pyran structures [86H935; 88JCR(S)146; 88TL2703] have been questioned (87H2811; 91TL5375).

The addition-cyclodehydration process [Eq. (6)] has been exploited for the preparation of various fused hetero-4*H*-pyrans, for example, **39a** (87AP223) and **40a**, where both alternative paths ($\text{R}^1, \text{X} = \text{Ph}, \text{CN}$; $\text{Y}, \text{R}^3 = -\text{CMe}=\text{N}-\text{NH}-$ or $\text{R}^1, \text{X} = -\text{CMe}=\text{N}-\text{NH}-$; $\text{Y}, \text{R}^3 = \text{CN}, \text{Ph}$) were applied (85S432). The addition-cycloaddition procedure [Eq. (7)] was similarly used to prepare 2(6)-amino-4*H*-pyrans **39b**



(**39a**) $\text{R} = \text{Ph}$; $\text{X} = \text{O}, \text{S}$

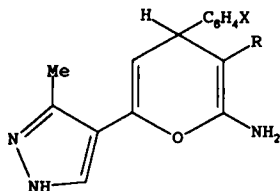


(**40a**) $\text{Ar} = 2\text{-furyl}$; $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{CN}$; $\text{R}^3 = \text{H}, \text{Ph}$

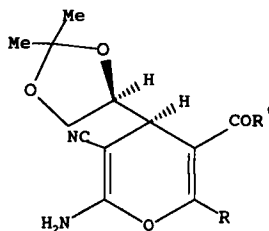
(**39b**) $\text{R} = \text{NH}_2$; $\text{X} = \text{O}, \text{S}$

(**40b**) $\text{Ar} = \text{Ph}$; $\text{R}^1 = \text{NH}_2$; $\text{R}^2 = \text{CONHNH}_2$; $\text{R}^3 = \text{H}$

(**40c**) $\text{Ar} = 2\text{-furyl}$; $\text{R}^1 = \text{OH}$; $\text{R}^2 = \text{CN}$; $\text{R}^3 = \text{H}, \text{Ph}$



(**41**) $\text{R} = \text{CO}_2\text{Et}, \text{CN}$; $\text{X} = \text{H}, 4\text{-Cl}$



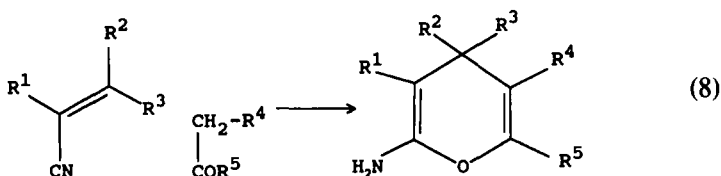
(**42**) $\text{R}, \text{R}^1: \text{Me}, \text{OEt}; \text{Me}, \text{OMe}; \text{Ph}, \text{OEt}$

(87AP223), **40b** (84JHC1885), **41** [85IJC(B)632], **45** ($R^1 = \text{CN}$, $R^2 = \text{Ph}$, XC_6H_4 where $\text{X} = 4\text{-Br}$, 4-Cl , 4-MeO , 3-NO_2 ; $R^3 = \text{Me}$; $R^4 = \text{H}$) (83ZOR2609), **47b** ($\text{Ar} = 2\text{-}$, 3- , $4\text{-MeOC}_6\text{H}_4$, $3,4\text{-(OCH}_2\text{O)C}_6\text{H}_4$; $\text{R} = \text{H}$, Cl , MeO , 1-naphthyl) [88JCR(S)10], **49a,b** (84ZOR2448), 2(6)-hydroxy-4*H*-pyrans **40c** (85S432), and some others (86EUP177965; 87AP223).

The approach of Eq. (7) has also been exploited for the asymmetric synthesis of prevailing amino-4*H*-pyrans **42** from (*R*)-2,3-*O*-isopropylidene glyceraldehyde via the corresponding chiral 2-acyl acrylates (92TL3809). Several reported **45**-like structures possessing 4-amino or 4-hydroxyl groups in the 4*H*-pyran ring (82H1637) should be considered with caution because convincing structure proof is lacking. Some attempts to introduce more complex heterocyclic substituents into the product molecules (90CCC524) should be corrected for the same reasons.

The second component in Eq. (7) can be replaced by the analogous thione derivative, as found in the synthesis of **43a** (85S432) and **45** ($R^1 = \text{CN}$, $R^2 = 4\text{-MeOC}_6\text{H}_4$, $R^3 = \text{Me}$, $R^4 = \text{Ph}$) [87ZN(B)107] accompanied by H_2S elimination.

b. *Two-Component Version from α,β -Unsaturated Nitriles*. This widely used process involving only addition and isomerization reaction steps proceeds according to general equation (8).



The variety of substituent patterns is shown in Table III. A number of fused 2(6)-amino-4*H*-pyrans were prepared in the same way, for example, **43b,c** (85S432), **44** (Table IV), **45** (Table V), **46a,b** (91LA827), **47a** (88CCC1534), **48** (86JHC93), and **49a,b** (83KGS277; 84ZOR2448). Only in rare cases were the reported 4*H*-pyran structures (86H935) questioned (87H2811). Some of the transformations have been reviewed (83H519).

In some cases, intermediate Michael adducts were trapped (83ZOR2609; 88ZOR460; 90ZOR1578) or used as starting components (88ZOR460; 89APR201).

Exceptional reaction routes have been observed in some cases. Thus, while cyano ester **50** reacted with **51a** to form **43b**, an unexpected cyclocondensation, $\mathbf{50} + \mathbf{51b} \rightarrow \mathbf{43d} + \text{H}_2\text{S}$, occurred. Similarly, attempts to pre-

TABLE III
2(6)-AMINO-4*H*-PYRANS PREPARED ACCORDING TO EQ.(8)

R ¹	R ²	R ³	R ⁴	R ⁵	References
EtO ₂ C	Ph	H	CN	Ph	86M247
EtO ₂ C	Ph	H	CN	PhCH=CH	85H2983; 86M247
EtO ₂ C	Ph	H	PhNHCO	PhNHCOCH ₂	86JHC1203
EtO ₂ C	4-MeOC ₆ H ₄	H	PhNHCO	PhNHCOCH ₂	86JHC1203
EtO ₂ C	2-thienyl	H	CN	Ph	83LA1468
CN	H	H	CN	Ph	91JCR(S)116
CN	2-furyl	H	CO ₂ Et	CH ₂ Cl	89CCC1336
CN	2-furyl	H	CO ₂ Et	Me	83ZOR164 ^a
CN	2-furyl	H	COMe	Me	86H935 ^b
CN	2-furyl	H	CN	Ph	83LA1468
CN	Ph	H	CO ₂ Et	Me	83ZN(B)639 ^c
CN	Ph	H	COMe	Me	86H935 ^d
CN	Ph	H	COPh	Ph	82ZOR625
CN	Ph	H	CN	Ph	86M247
CN	Ph	H	CN	PhCH=CH	85H2983; 86M247
CN	Ph	H	PhNHCO	Me	89APR201 ^e
CN	3-BrC ₆ H ₄	H	CO ₂ Et	Me	82ZOR625
CN	4-XC ₆ H ₄ ^f	H	PhNHCO	Me	89APR201 ^e
CN	XC ₆ H ₄ ^g	H	CO ₂ Et	Me	86H935; 89LA585
CN	2-pyridyl	H	COMe	Me	90IJC(B)322
CN	2-pyridyl	H	CO ₂ Et	Me	90IJC(B)322
CN	2-thienyl	H	CN	Ph	83LA1468
CN	2-thienyl	H	COMe	Me	90IJC(B)322
CN	2-thienyl	H	CO ₂ Et	Me	88AP131 ^h
CN	Ph	Me	CN	Ph	90JCR(S)310
CN	Ph	Et ⁱ	CN	Ph	90JCR(S)310
CN	Ph	Me	CO—O—CH ₂		91LA827
CN	4-XC ₆ H ₄ ^j	Me	CN	XC ₆ H ₄ ^k	90JCR(S)310
CN	5-X-2-furyl ^l	H	COMe	Me	90CCC718
CN	5-XYC ₆ H ₃ -2-furyl ^m	H	CO ₂ Et	Me	83ZOR164
PhNHCO	4-MeOC ₆ H ₄	H	COMe	Me	83AP822
PhNHCO	4-MeOC ₆ H ₄	H	CO ₂ Et	Me	83AP822
2-BTH ⁿ	Ph	H	CO ₂ Et	Me	88AP509

^a See also 86H935, 88AP131, and 90IJC(B)322.

^b See also 90CCC718 and 90IJC(B)322.

^c See also 84JHC1261, 86H935, 86ZN(B)925, and 87JHC1677.

^d See also 87JHC1677, 87H2811, 88T5861, 91JPR345, and 92T1581.

^e Michael intermediates were isolated.

^f X = Cl, Me, MeO, and O₂N.

^g X = 2-Cl, 4-Cl, and 4-MeO.

^h See also 90IJC(B)322.

ⁱ No pyrans were obtained for R³ = *t*Bu and Ph.

^j X = Cl, Me, MeO, and O₂N.

^k X = 4-Cl, 4-Me, and 3-O₂N.

^l X = H, Me, MeO₂C, PhO, and PhS.

^m X, Y = H, H; 2-Cl, H; 3-O₂N, H; and 4-Me, 3-O₂N.

ⁿ 2-Benzothiazolyl.

TABLE IV
 2(6)-AMINO-4H-PYRANS **44** PREPARED FROM 1,3-CYCLOHEXADIONES

R ¹	R ²	R ³	R ⁴	X,Y	References
CO ₂ Et	X-2-furyl	H	H	H, 5-Br, 5-Br, 5-I, 5-O ₂ N	83ZOR164
CO ₂ Et	X-C ₆ H ₄ -2-furyl	Me	Me	2-Cl	83ZOR164
CO ₂ Et	X,Y-C ₆ H ₃ -2-furyl	H	H	H,H; 4-Br,H; 2-Cl,H; 3-Cl,4-Cl; 4-O ₂ N,H; 4-Me,3-O ₂ N	83ZOR164
CO ₂ Et, CN	X-C ₆ H ₄	H	H	H, 3-Br, 4-Cl, 3-F, 4-F	82ZOR625; 86ZOR1315
CN	Ph	H	H	—	90LA101
CO ₂ Et, CN	Ph	H	Ph	—	86ZOR1315
CO ₂ Et, CN	X-C ₆ H ₄	Me	Me	H, 3-Br, 2-Cl, 4-Cl, 3-F, 4-F, 4-MeO	82ZOR625 86ZOR1315 89JPR971
CSNH ₂	X-C ₆ H ₄	Me	Me	4-Br, 4-F	88ZOR460
CN	X-2-furyl	H	H	5-Br, 5-O ₂ N	83ZOR164
CN	X-2-furyl	Me	Me	H, 5-I	83ZOR164
CN	X,Y-C ₆ H ₃ -2-furyl	H	H	H,H; 4-Br,H; 2-Cl,H; 4-O ₂ N,H; 3-Cl,4-Cl; 4-Me,3-O ₂ N	90LA101
CN	X,Y-C ₆ H ₃ -2-furyl	Me	Me	H,H; 4-Br,H; 2-Cl,H; 3-Cl,4-Cl; 4-Me,3-O ₂ N	83ZOR164
NO ₂	X,Y-C ₆ H ₃	Me	Me	H,H; 4-Cl,H; 4-F,H; 3-HO,H; 4-HO,H; 3-MeO, 4-MeO; 3-Me,H; 2-Me, 4-Me; 2-Me,5-Me; 2-MeO, H; 3-MeO,H; 4-MeO,H; 4-Me ₂ N, H	84ZOR2481; 86DOB51
NO ₂	2-furyl	Me	Me	—	84ZOR2481
NO ₂	2-thienyl	Me	Me	—	84ZOR2481
NO ₂	X-3-indolyl	Me	Me	2-PhCH ₂	84ZOR2481
CSNH ₂	X-C ₆ H ₄	Me	Me	4-Br, 4-F	88ZOR460 ^a 90ZOR1578

^a Intermediate adducts were trapped at 0–5°C.

pare amino-4H-pyran **45** (R¹ = CO₂Et, R² = 2-furyl, R³ = Me, R⁴ = H, Ph) from cyano ester **50** resulted in other products for which structure **40c** was proposed (85S432).

Recently, cycloaddition [Eq. (8)] has been exploited for the synthesis of asymmetric 4-enantio-substituted amino-4H-pyrans **52**. As in **42**, the prevailing isomers exhibited the *R*-configuration at position 4 (93TL5627).

TABLE V
2(6)-AMINOIMIDAZO-4H-PYRANS **45** PREPARED ACCORDING TO EQ.(8)

R ¹	R ²	R ³	R ⁴	References
CN	Ph	Me	Ph	82ZOR625 ^a
CN	Ph	NH ₂	Ph	83JHC667
CN	XC ₆ H ₄ ^b	Me	H	83ZOR2609 ^c
CN	X-4-MeOCH (X = 2-MeO, 3-HO)	Me	H	83ZOR2609 ^c
CN	2-furyl	Me	H	83ZOR164 ^d
CN	2-furyl	Me	Ph	85S432
CN	2-furyl	NH ₂	H	87AP223
CN	5-(4-Me-3-O ₂ NC ₆ H ₃)-2-furyl	Me	H	83ZOR164
CN	5-X-2-furyl (X = Br, I, NO ₂)	Me	H	83ZOR164
CN	3-pyridyl	NH ₂	H	90IJC(B)322
CN	2-thienyl	NH ₂	H	87AP223 ^e
CONHNH ₂	Ph	Me	H	84JHC1885
NO ₂	Ph	Me	Ph	84ZOR2481

^a See also 83ZOR2609.

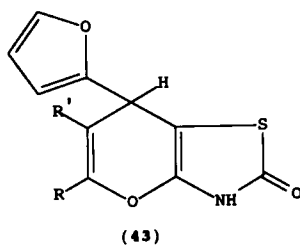
^b X = 3-Br, 4-Br, 2-Cl, 4-Cl, 4-Et₂N, 2-F, 3-F, 4-F, 2-Me, 4-Me, 2-MeO, 4-MeO, 2-NO₂, 3-NO₂, 4-NO₂, 3-OH, 4-OH.

^c Some Michael adducts were isolated at 20°C.

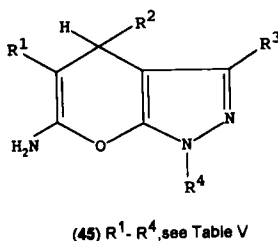
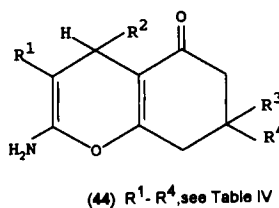
^d See also 85S432.

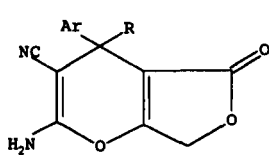
^e See also 90IJC(B)322.

A reported preparation of 2-amino-3-cyano-4-phenyl-6-(2-thiazolyl)-4H-pyran from PhC(Me)=C(CN)₂ and 2-thienylcarbaldehyde [87CI(L)60] had to be conditioned by an additional dehydrogenation process, however.

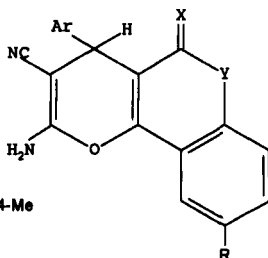


- (a) R = Ph; R' = CN
 (b) R = NH₂; R' = CO₂Et
 (c) R = NH₂; R' = CN
 (d) R = EtO; R' = CN

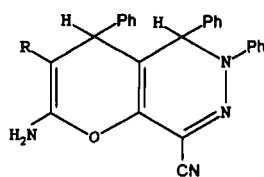




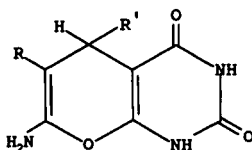
(46a) Ar = Ph; XC_6H_4 (X: 2-Cl, 4-Cl, 4-Me, 4- NO_2); 2-thienyl; R = H
(46b) Ar = Ph, R = Me



(47a) Ar = Ph, 4-MeOC $_6\text{H}_4$; R = H; X = O; Y = NH
(47b) Ar, R see text; X = H $_2$; Y = S



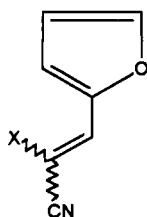
(48) R = CO $_2$ Et, CN



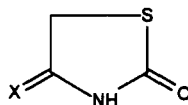
(49a) R = CO $_2$ Et; R' = Ph, 4-ClC $_6\text{H}_4$, 4-FC $_6\text{H}_4$

(49b) R = CN; R' = Ph, XC_6H_4
X: 4-Br, 4-Cl, 3-F, 4-F, 2- NO_2 , 3- NO_2 , 4- NO_2

c. *Three-Component Versions.* Cyclocondensation [Eq. (9)] was used for the preparation of further amino-4*H*-pyrans—namely, **45** ($\text{R}^1 = \text{CN}$; $\text{R}^2 = \text{Ph}$, XC_6H_4 where X = 4-Br, 4-Cl, 4-F, 4-MeO, 4-Me $_2\text{N}$, 3- NO_2 , 2,4-(MeO) $_2\text{C}_6\text{H}_3$; $\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{H}$) (83ZOR2609), **53a,b** (92G299), **53c**

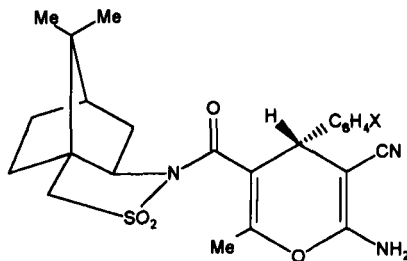


(50) X = COOEt



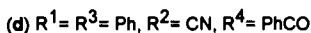
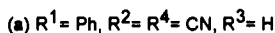
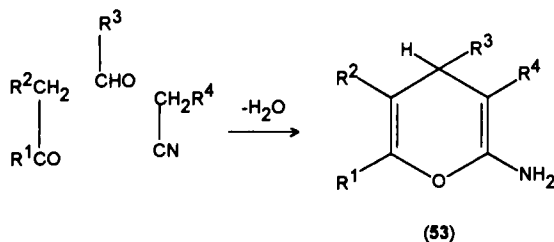
(51a) X = O

(51b) X = S



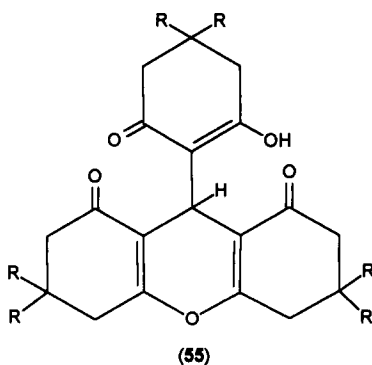
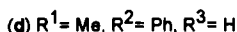
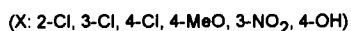
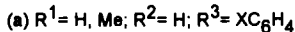
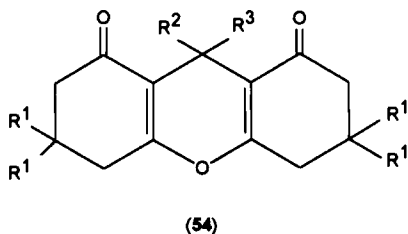
(52) X = H, 4-Br, 4-Cl, 2-Me, 4-Me, 3- NO_2

(85CPB3787), and **53d** (83H2393)—by heating the components with piperidine in EtOH or *i*PrOH. The same procedure starting from $\text{XC}_6\text{H}_4\text{CHO}$, $\text{CH}_2(\text{CN})_2$ or $\text{NCCH}_2\text{COO}_2\text{Et}$ and dimedone, and 1,3-cyclohexadione or 5-phenyl-1,3-cyclohexadione led to the same products **44** as those of the two-component versions summarized in Table IV (86ZOR1315).



(9)

The well-known cyclocondensation of aldehydes with two molecules of dimedone or similar 1,3-cyclohexadiones has been accomplished with other aldehyde-like compounds. Thus, dinitriles $\text{XC}_6\text{H}_4\text{CH}=\text{C}(\text{CN})_2$ were used instead of substituted benzaldehydes for the preparation of 4H-pyrans **54a** (92ZY241). α -Keto carboxylic acids MeCOCO_2H and $\text{HO}_2\text{C}(\text{CH}_2)_2\text{COCO}_2\text{H}$ similarly gave analogous products **54b,c** while the use of PhCOCO_2H led to decarboxylation product **54d** together with other nonpyran compounds ([86IJC(B)347]. The reaction with ethyl ortho-



formate was observed to involve three molecules of a given 1,3,-cyclohexadione, affording 4*H*-pyrans **55** (93JA872).

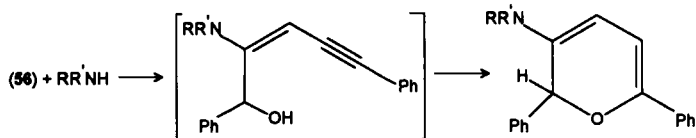
C. FROM ACETYLENES

Novel possibilities consisting in exploitation of coordination catalysis have been introduced. In addition, the traditional Diels–Alder cycloaddition reaction has been used in the last decade.

1. Preparation of 2*H*-Pyrans

Some 2*H*-pyrans were obtained by cyclization of alkenic acetylenes after their activation involving $C\equiv C \rightarrow C=C$ exchange in initial reaction steps. Thus, diacetylenic alcohol $\text{PhCH}(\text{OH})\text{C}\equiv\text{C}-\text{C}\equiv\text{CPh}$ (**56**) was found to cyclize to 2*H*-pyrans readily after the addition of secondary amines $\text{RR}'\text{NH}$ (82CZ296). Similarly, acetylenic ketone $\text{PhCOC}\equiv\text{C}-\text{CH}=\text{CHOMe}$ (**57**) gave appropriate 2*H*-pyrans after the addition of aqueous bromine or benzthiamide (83AP454).

A new approach to 2*H*-pyrans has been found in various



$\text{R, R}' = (\text{CH}_2)_4; \text{O}(\text{CH}_2\text{CH}_2)_2; \text{HN}(\text{CH}_2\text{CH}_2)_2; 2\text{-MeOC}_6\text{H}_4\text{N}(\text{CH}_2\text{CH}_2)_2; \text{c-C}_6\text{H}_{11}; 2,6\text{-diphenyl-2H-pyran-3-yl}$

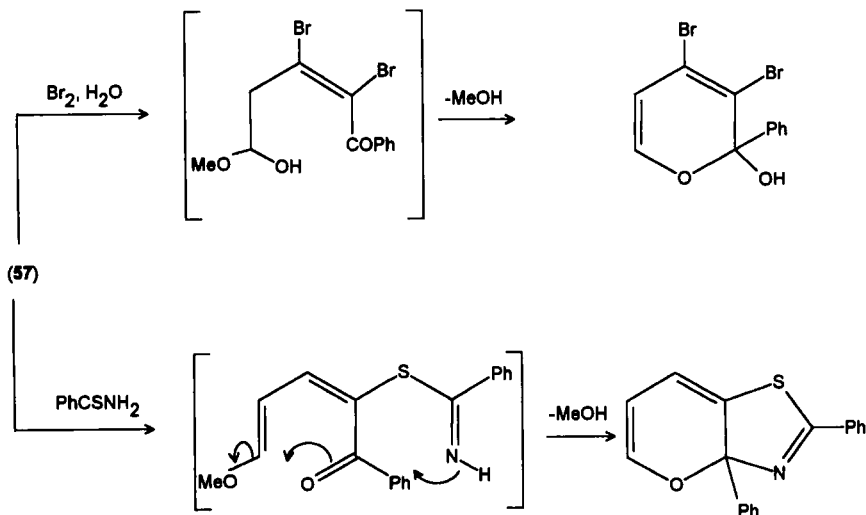
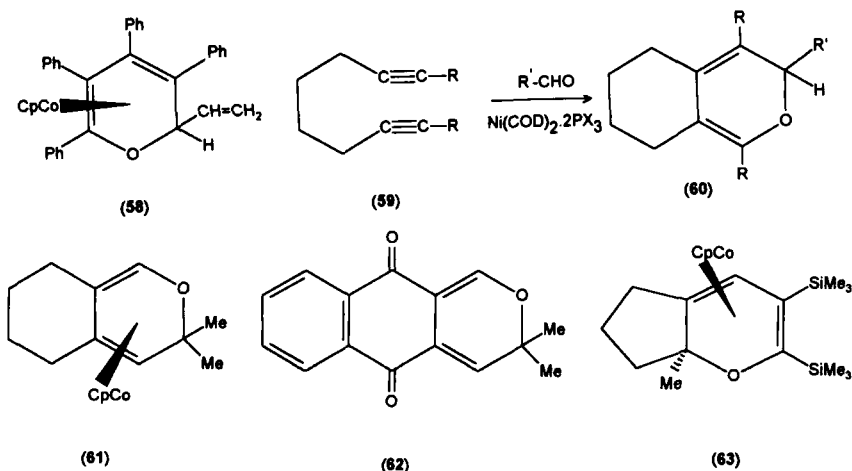


TABLE VI
RESULTS OF COORDINATION-CATALYZED REACTION **59** → **60** (88JA8570)

R	R'	X	Yield (%)	R	R'	X	Yield (%)
Bu	Ph	C ₆ H ₁₁	78	Et	<i>i</i> Pr	C ₆ H ₁₁	69
Me	Ph	<i>t</i> Bu	52	Et	Ph	C ₆ H ₁₁	79
Me	Ph	C ₆ H ₁₁	39	Et	Ph	Bu, Ph	79
Et	Pr	C ₆ H ₁₁	90	Et	Me	C ₆ H ₁₁	28

$[2\pi + 2\pi + 2\pi]$ -cycloadditions of two acetylenic and one carbonyl moiety. The success of the procedure usually requires coordination catalysis and eventually additional photochemical activation. The transformations, undoubtedly occurring in ligand fields of transition metals, have been accomplished in intermolecular three- and two-component versions as well as in intramolecular one-component processes. Thus, *2H*-pyran **58** was prepared in 55% yield by the cycloaddition of two diphenylacetylene molecules to acrylaldehyde in a methyl acetate solution of CpCo(C₂H₄)₂ (Cp = cyclopentadiene) at 20°C (87PSC39). Fused *2H*-pyrans **60** were obtained in various yields (Table VI) from corresponding diacetylene components **59** using Ni(COD)₂-PX₃-like catalysts (88JA8570). On the other hand, the procedures based on heating and/or UV illumination with CpCo(CO)L or CpCo(C₂H₄) catalysts led to CpCo-coordinated *2H*-pyrans, mainly in mixtures with their open valence isomers and other photoproducts. For example, 41% of **61** but only 1% of **62** together with 4% of the coordinated species is reported in the case of another CpCo(CO) (MA) catalyst (89SL15). The yields of coordinated product **63** obtained by the alternative two-component addition of acetylenic partners HC≡C(CH₂)₃COMe and Me₃SiC≡CSiMe₃ were found to depend strongly



(6–86%) upon the choice of ligands in the catalysts and experimental conditions (89SL15). An interesting cyclodimerization of cycloalkanones giving moderate yields of exotic 2*H*-pyrans **64** has been reported, too (89TL2893).

One-component intramolecular versions have been investigated using the precursors $\text{HC}\equiv\text{C}(\text{CH}_2)_4\text{C}\equiv\text{C}(\text{CH}_2)_{3,4}\text{COR}$ where $\text{R} = \text{H}$ or Me . The typical coordination products exhibited 2*H*-pyran, dienone, or dienal structures **65**, **66**, and **67**, respectively (Table VII). The free 2*H*-pyrans could be obtained from **65** with a mixture of $\text{CuCl}_2 \cdot \text{H}_2\text{O}$, Et_3N , and MeCN (89SL15). Alternative detailed mechanisms of the coordination catalysis has been considered (88JA8570).

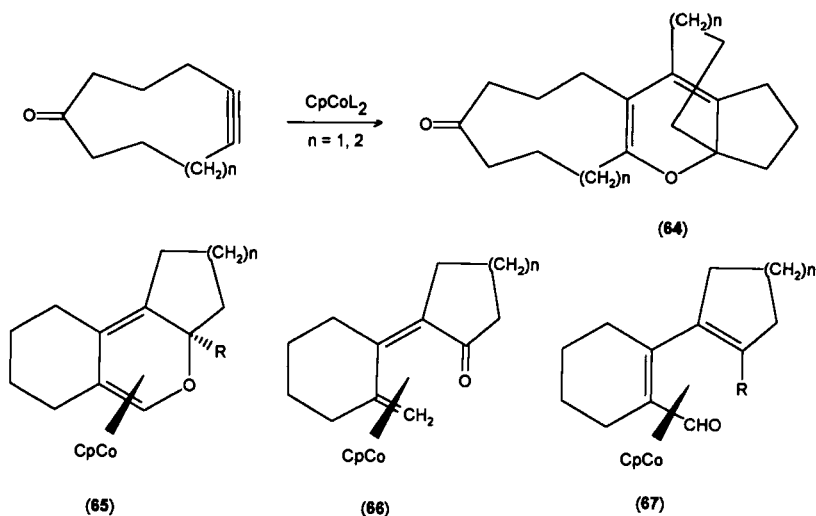


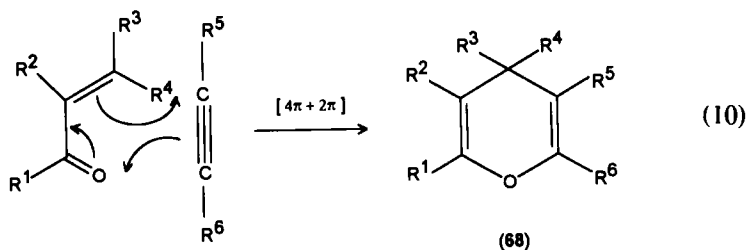
TABLE VII
PRODUCTS FROM ACETYLENIC PRECURSORS $\text{HC}\equiv\text{C}(\text{CH}_2)_4\text{C}\equiv\text{C}(\text{CH}_2)_n\text{C(R)=O}$

<i>n</i>	R	Catalyst ^a	Yield (%)			References
			65	66	67	
1	H	CpCo(COD)	8	—	—	89TL2893
1	H	CpCo(CO) ₂ , <i>hν</i>	5	33	—	89SL15
1	H	CpCo(C ₂ H ₄)	7	44	—	89SL15
1	Me	CpCo(CO) ₂ , <i>hν</i>	69	—	22	89SL15
2	H	CpCo(COD)	45	—	—	89TL2893
2	H	CpCo(CO) ₂ , <i>hν</i>	25	25	—	89SL15
2	H	CpCo(C ₂ H ₄)	34	14	—	89SL15
2	H	CpCo(CO) ₂ , <i>hν</i>	25	25	—	89SL15
2	Me	CpCo(CO) ₂ , <i>hν</i>	57	—	17	89SL15

^a Cp = cyclopentadienyl, COD = cycloocta-1,5-diene.

2. Preparation of 4H-Pyrans

The most popular Diels–Alder procedures have traditionally been based on the $[4\pi + 2\pi]$ -cycloaddition of α,β -unsaturated carbonyl compounds with appropriate acetylenic partners according to Eq. (10). The newly reported 4H-pyrans **68** (86JOC1199; 87ZOR1644; 92TL699) are shown in Table VIII. Process (10) usually can be accomplished by heating in suitable solvents such as THF (92TL699) and xylene (90ACS833) or by TiCl_4 catalysis (86JOC1199).



Spirocyclic 4H-pyrans **69a** (90ACS833) and **69b** were prepared in the same way. In the case of **69b** the starting α,β -unsaturated component was generated *in situ* from enolacetate **70** (89CB1285). Analogous procedures with $\text{HC}\equiv\text{COEt}$ were used for the preparation of other spirocyclic products **71** and **72** (89CB1285).

Attempts to realize cycloaddition (10) with 2-methylene-1,3-cyclopentadione and $\text{HC}\equiv\text{COEt}$ failed owing to the kinetic lability of product **68**

TABLE VIII
4H-PYRANS **68** PREPARED ACCORDING TO EQ.(10)

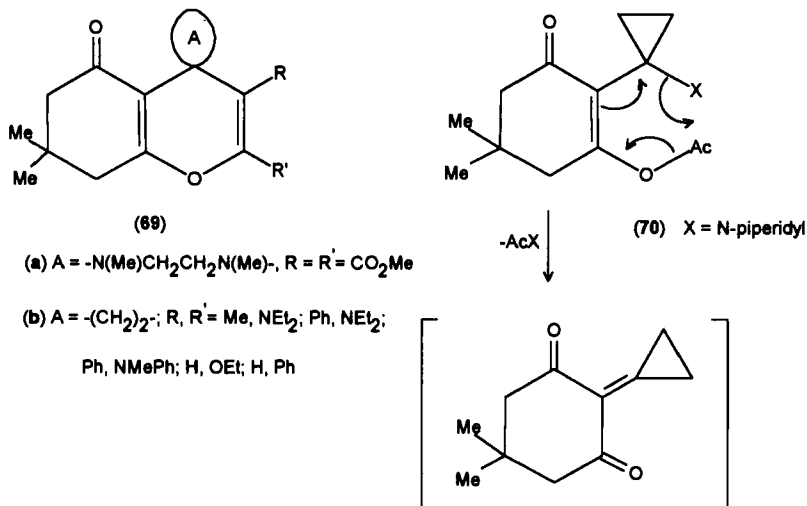
R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	References
H	CHO	Ph	H	H	Ph	?	87OSM191
CN	H	Me	Me	SiMe_3	Me	10	83TL1395
CN	H	Me	H	SiMe_3	$\text{CMe}_2\text{OSiMe}_3$	10 ^a	86JOC1199 ^b
Me	H	H	H	$\text{CH}=\text{CHMe}$	NEt_2	62	87ZOR1644
Me	H	H	H	$\text{CH}=\text{CMe}_2$	NEt_2	64	87ZOR1644
Me	CO_2Et	Ph	H	CO_2Me	N-piperidyl	90	92TL699
EtO	CO_2Et	Ph	H	CO_2Et	N-piperidyl	60 ^c	92TL699
Ph	CO_2Et	Ph	H	CO_2Me	N-piperidyl	62	92TL699
Ph	COMe	Ph	H	CO_2Me	N-piperidyl	28	92TL699
Ph	COMe	Ph	H	CO_2Me	N-pyrrolidinyl	15	92TL699

^a In addition to 10% **68** where $\text{R}^6 = \text{CMeOH}$ (86JOC1199).

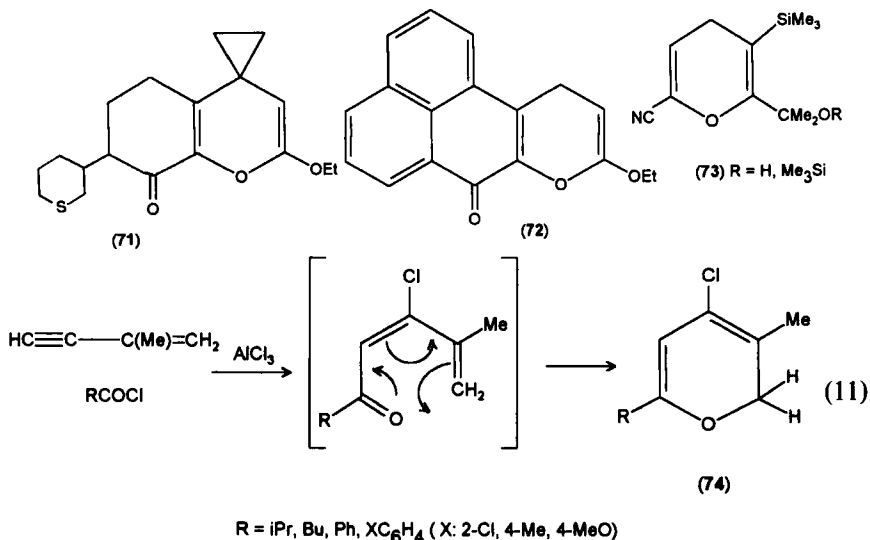
^b See also 83TL1395.

^c In addition to 20% of a $[2\pi + 2\pi]$ adduct.

toward the starting dione (88JOC4038). Only low yields (10%) of 4*H*-pyrans **73** were obtained after the reaction of the acetylene component $\text{Me}_3\text{SiC}\equiv\text{CCMe}_2\text{OSiMe}_3$ with acyl cyanide (*E*)- $\text{MeCH}=\text{CHCOCN}$ (83TL1395; 86JOC1199).



The AlCl_3 -catalyzed addition of acyl chlorides to acetylenic hydrocarbon $\text{HC}\equiv\text{C}-\text{C}(\text{Me})=\text{CH}_2$ was observed to lead to mixtures of products containing (*E*)-dienones, which spontaneously isomerized according to Eq. (11) to corresponding 2*H*-pyrans (90ZOR965).



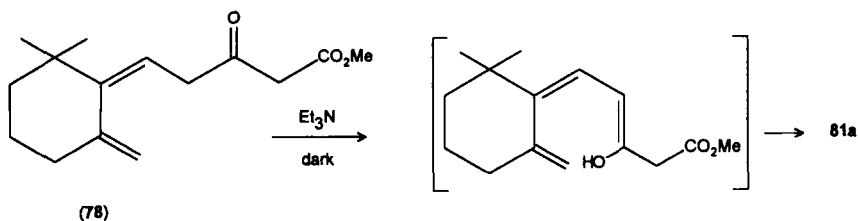
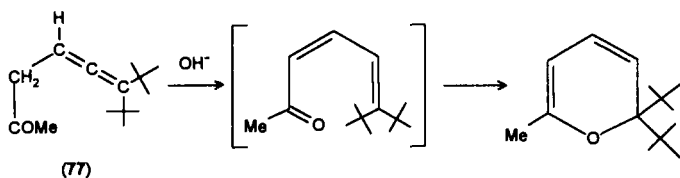
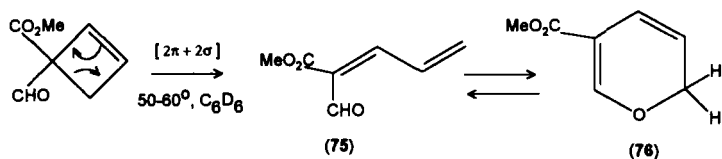
D. FROM DIENALS AND DIENONES

This approach to various 2*H*-pyrans involving generation of the title precursors *in situ* is mentioned earlier in Section III.B,C. Hence we consider here cases in which (*Z*)-dienals or (*Z*)-dienones capable of cyclization to 2*H*-pyrans [83AHC(34)145) are generated by isomerization procedures.

1. Thermal Isomerizations

This type of isomerization still seems to be of limited importance. For example, a mixture of unseparable valence-bond isomers **75** and **76** was obtained by thermolysis of an appropriate cyclobutene precursor (92TL883). Another 2*H*-pyran intermediate postulated in the *Z*-*E* interconversion of stereoisomeric retinals could be neither isolated nor identified (92JOC1110).

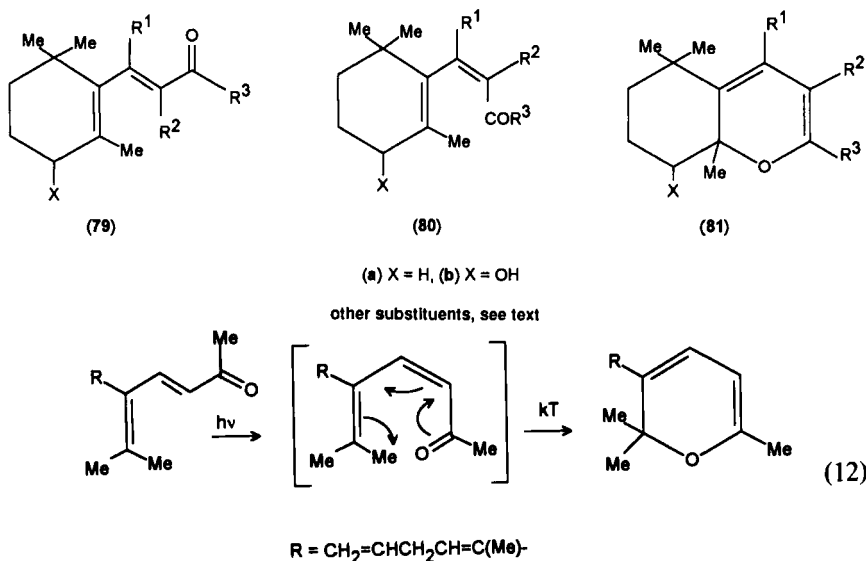
Somewhat better results were achieved using two ketonic precursors. Allenic keton **77** gave 45% of 2,2-di-*tert*-butyl-6-methyl-2*H*-pyran by base catalysis (91CB2633). Similarly, keto ester **78** was converted to isomeric 2*H*-pyran **81a** ($R^1 = R^2 = H$; $R^3 = CH_2CO_2Me$) presumably via the corresponding enol (85JOC1939).



Another case of such cyclizations, accompanied, however, by replacement of 2-alkylthio groups (84BCJ734), will be discussed in Section V.D.1 (Scheme 8).

2. Photoisomerizations

The photochemical path to 2*H*-pyrans may be illustrated by the example shown in Eq. (12), which yields 73% of product (81HCA1235). Much more investigation has been done, however, on the phototransformations of starting β -ionone **79a** ($R^1 = R^2 = H$, $R^3 = Me$) and its derivatives **79a,b** according to the scheme **79** \rightarrow **80** \rightarrow **81** (see Table IX).



While the three-membered ring in bicyclic precursors **82** ($R^1 = R^2 = H$; $R^3 = Me$) was found to be photochemically stable (81HCA1235), the oxirane ring in epoxides **83** ($R^1, R^2, R^3 = H, H, Me; H, Me, Me; Me, Me, Me$) was observed to be photochemically cleaved (**83** \rightarrow **79b**) prior to the formation of (*Z*)-dienone **80b** and 2*H*-pyran **81b** (85HCA192). If both the substructural patterns mentioned, or two oxirane rings, were present in the starting β -ionone-like molecules, the six-membered carbocycle was completely destroyed and moderate yields of 2*H*-pyrans **84a,b** together with other photoproducts were obtained (84HCA815; 85HCA1583).

TABLE IX
PHOTOISOMERIZATIONS OF β -IONONE-LIKE (E)-DIENONES

Starting composition	R ¹	R ²	R ³	Products ^a		References
				(Z)-dienone	2H-pyran	
79a	H	H	Me	+	+	81T1571 ^b
79a	H	H	Bu	—	+	83RTC355
79a	H	H	<i>t</i> Bu	—	+	83RTC302
79a	H	H	CH ₂ C(Me)OH	—	+	88JMC713
79a	H	H	CH ₂ CO ₂ Me	—	+	85JOC1939
79a	H	H	CH(Me)CO ₂ Me	—	+	83CL651
79a	H	H	CH(CO ₂ Me)CH ₂ CO ₂ Me	—	+	83CL651
79a	H	H	PhCH=CH	—	+	89SC1759 ^c
79a	H	H	4-XC ₆ H ₄ CH=CH ^d	—	+	89SC1759 ^c
79a	H	H	3,4-(MeO) ₂ -C ₆ H ₃ CH=CH	—	+	89SC1759
79a	H	H	2-furylCH=CH	—	+	89SC1759
79a	H	Me	Me	+	+	84HCA1175
79b ^e	H	H	Me	—	+ ^f	85HCA192
79b ^e	H	Me	Me	+	+	85HCA192
79b ^{e,f}	Me	Me	Me	+	—	85HCA192
82	H	H	Me	+	+	81HCA1235

^a Isolated or detected (+); not observed (—).

^b See also 84HCA1175.

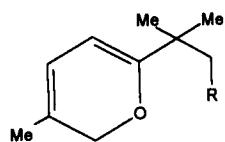
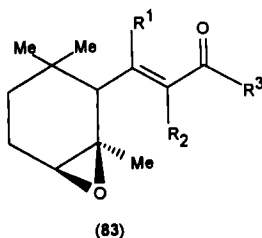
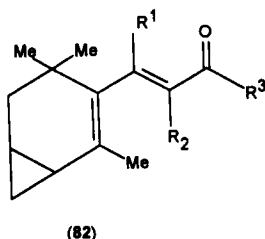
^c Preliminary communication: 88CC1024.

^d X = Br, Cl, F, Me, MeO, O₂N, NC.

^e Generated *in situ*.

^f Mixtures of diastereoisomers.

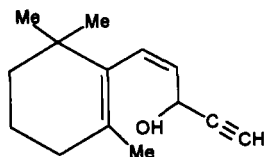
In a case of vicinal acetoxy–hydroxy substitution, the photodehydration affording 2H-pyran **81** (R¹ = R² = H; R³ = Me; X = AcO) was reported (80NNK1833).



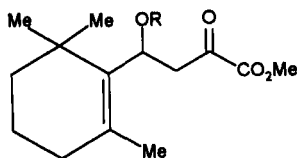
3. Other Preparations

Some (Z)-dienones were generated *in situ*, affording the expected 2H-pyrans. While oxidation of the hydroxy precursor **85** with MnO₂ gave

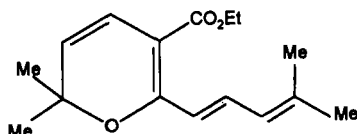
acetylenic product **81** ($R^1 = R^2 = X = H$, $R^3 = HC\equiv C-$) in 45% yield (85JA1034), only a mixture containing 16% of methyl ester **81** ($R^1 = R^2 = X = H$; $R^3 = MeO_2CCH_2$) was obtained after the reaction of keto ester **86** with stannic chloride (85JOC1939). Analogously, the reaction of $MeCH=CHCHO$ with the Wittig reagent $Ph_3P=CHCOCH_2CO_2Et$ gave only 18% of a fraction containing 82% of 2*H*-pyran **87** in equilibrium with isomeric (*Z*)-dienone (87TL4721).



(85)



(86)



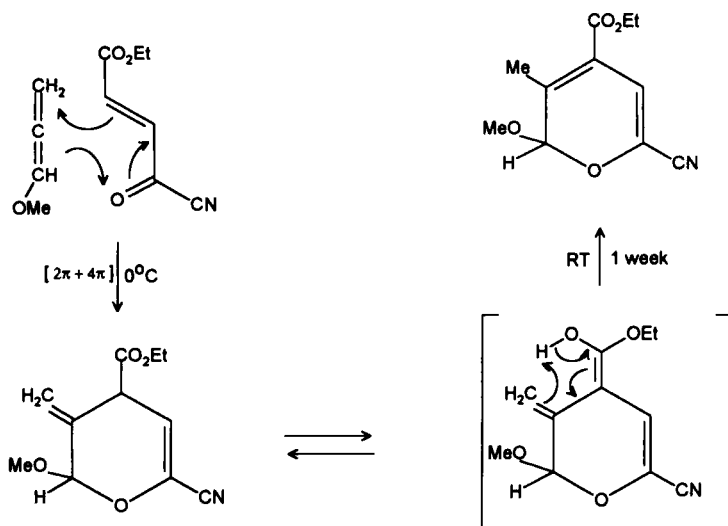
(87)

E. FROM OTHER ACYCLIC PRECURSORS

Various Diels–Alder cycloadditions with α,β -unsaturated carbonyl compounds have been observed to afford pyrans, provided the primary adducts are capable of isomerization or subsequent easy elimination of HX .

The first type of reaction has been accomplished with $MeOCH=C=CH_2$ as the dienophile according to Scheme 4 (91CB1425).

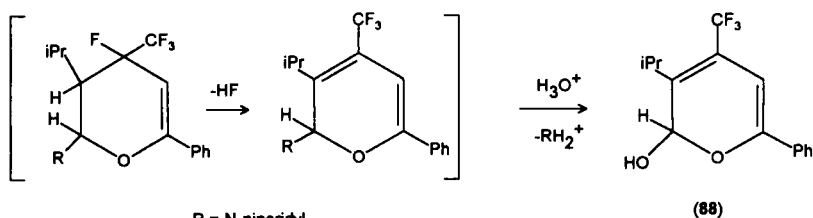
The second type of reaction can lead either to 2*H*- or to 4*H*-pyrans, depending on the partners to which the leaving group X is bound. Thus, 2*H*-pyran **88** was obtained from fluorinated ketone $PhCOCH=CFCF_3$ ($X = F$) and enamine $iPrCH=CHN(CH_2)_5$ after acidic hydrolysis of intermediates (82TL1471). More often, the leaving group ($X = Me_3SiO$, *N*-morpholyl) was bound to the α,β -unsaturated component, and then the cyclization proceeded according to Scheme 5. The reported results are summarized in Table X. The reactions were performed by heating (93CL631) or with $TiCl_4$ catalysis (84TL4503). In the case of the more reactive substituents ($R^1 = NCO$), a subsequent addition of HX affording final products with $R^1 = XCONH$ has been observed (93CL631).



SCHEME 4

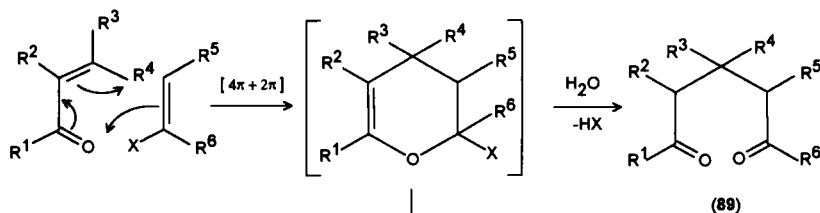
When two leaving groups were bound to the diene partner $\text{Me}_3\text{SiCH}=\text{CHCH}=\text{CHOAc}$ ($\text{X}^1 = \text{Me}_3\text{Si}$; $\text{X}^2 = \text{AcO}$), its cycloaddition with dienophile $\text{O}=\text{C}(\text{CO}_2\text{Et})$ yielded only 12% of the expected 2,2-bis-ethoxycarbonyl-2H-pyran (82JA2308).

The 6-*tert*-butyldimethylsilyloxy derivative of tetrahydro-5H-chromen



R = N-piperidyl

(88)



(89)

68

SCHEME 5

TABLE X
 CYCLIZATION REACTIONS PROCEEDING ACCORDING TO SCHEME 6

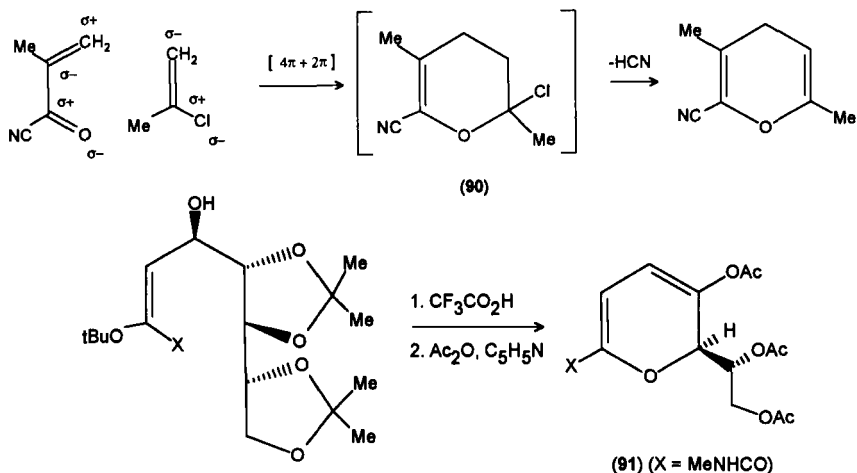
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	X	Products
Me	H	H	H	CN	Ph	OSiMe ₃	68 ^a
CN	H	Me	H	—(CH ₂) ₃ —		OSiMe ₃	89 + 68 ^b
CN	H	Ph	H	—(CH ₂) ₃ —		OSiMe ₃	89 + 68 ^b
CN	Me	H	H	—(CH ₂) ₃ —		OSiMe ₃	89 + 68 ^b
CN	H	Me	H	—(CH ₂) ₄ —		OSiMe ₃	89 + 68 ^b
CN	H	Me	Me	—(CH ₂) ₄ —		OSiMe ₃	89 + 68 ^b
CN	Me	H	H	—(CH ₂) ₄ —		OSiMe ₃	89 + 68 ^b
NCO	Me	H	H	Me	Ph	<i>N</i> -morpholyl	68 ^c
NCO	Me	H	H	—(CH ₂) ₄ —		<i>N</i> -morpholyl	68 ^c

^a Reference 86TL2027.^b Reference 84TL4503.^c Reference 93CL631, see text.

81 (R¹ = R² = H, R³ = Me) was obtained in 4% yield among other products from hexatriene precursors (91TL7005).

2-Cyano-3,6-dimethyl-4*H*-pyran was isolated in 60% yield in attempts to generate α,β -unsaturated acyl cyanide by the substitution of H₂C=C(Me)COCl with CuCN to give H₂C=C(Me)COCN and CuCl, but the structure of the 4*H*-pyran is not well explained by the postulated (83TL2847; 86JOC1199) mechanism. An alternative route involving initial decarbonylation (H₂C=C(Me)COCl → H₂C=C(Me)Cl + CO) and subsequent cycloaddition leading to intermediate **90** appears to be a more acceptable version.

An interesting optically active 2*H*-pyran **91** was found to arise after



elimination of the protecting groups and subsequent acetylation of the appropriate sugar derivative (89LA69).

2-Hydroxy-3-isopropyl-4-trifluoromethyl-6-phenyl-2*H*-pyran was obtained in 24% yield after a spontaneous reaction of $\text{PhCOCH}=\text{CFCF}_3$ with enamine $i\text{PrCH}=\text{CHN}(\text{CH}_2)_5$ at room temperature. A probable mechanism has been discussed (85NKK2146).

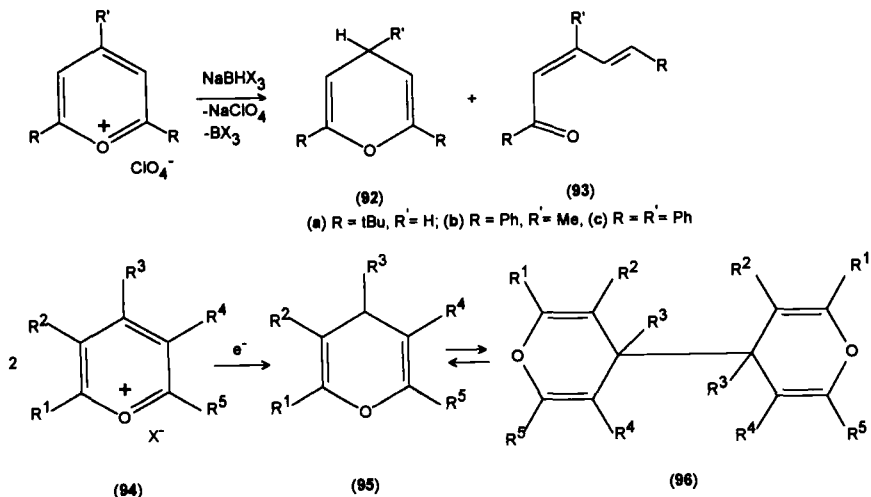
IV. Synthesis from Cyclic Precursors

A. FROM PYRYLIUM SALTS

This widely used approach to pyrans has been applied frequently in the last decade. In addition to the preceding article [83AHC(34)145], other reviews involving the conversions of pyrylium salts are available [82AHC(3)140; 92MOCH755]. Although most of those transformations are nucleophilic additions, some may be of a radical nature.

1. Reductions

Only a few examples of hydride-like reductions affording pyrans have been reported. Thus, a small amount (24%) of 2,6-di-*tert*-butyl-4*H*-pyran (**92a**) together with isomeric dienone **93a** (18%) was isolated after the reaction of the starting perchlorate with NaBH_4 (87CCC1305). Similar results were obtained with 4-methyl-2,6-diphenyl- and 2,4,6-triphenylpyrylium perchlorates using the $\text{NaBH}(\text{Ac})_3$ reagent prepared *in situ*, giving mixtures **92b** (47%) and **93b** (28%) or **92c** (13%) and **93c** (77%), respectively (87TL1341). Replacement of the 2- or 2,6-phenyl groups in the starting



pyrylium salts by primary or secondary alkyls led to dihydro- and/or tetrahydropyran derivatives (87TL1341; 88OPP231).

2,6-Disubstituted pyrylium perchlorates could be successfully reduced to 4*H*-pyrans **92** ($R = \text{Ph}$, 4-MeOC₆H₄; $R' = \text{H}$) with some tertiary amines (81JHC1235); see Section IV.A.4.

A number of new one-electron reductions of salts **94** ($X = \text{BF}_4$) to dimeric 4*H*-pyrans **96** via monomeric radicals **95** have been described. The conversions of the tetrafluoroborates **94** ($R^1, R^2, R^3, R^4, R^5 = \text{Ph}, \text{Ph}, \text{H}, \text{Ph}, \text{Ph}; \text{Ph}, \text{Me}, \text{Ph}, \text{H}, \text{Ph}; \text{Ph}, \text{Ph}, \text{Ph}, \text{H}, \text{Ph}; \text{Ph}, \text{Ph}, \text{Ph}, \text{Ph}, \text{Ph}; 4\text{-MeOC}_6\text{H}_4, \text{H}, 4\text{-MeOC}_6\text{H}_4, \text{H}, 4\text{-MeOC}_6\text{H}_4$) to corresponding dimers **96** were accomplished with Zn granules in THF [86NJC345; 89BCJ2279; 89JPP(A)171]. A photochemical version of the process using THF, Ph₃P, or hexamethylbenzene as reducing agents was also successful (89BCJ2279) as was reduction in a poly(*N*-vinylcarbazole) matrix (82ZNP452). Several electrochemical investigations on **94**-like salts have confirmed the same one-electron reduction paths; e.g., $2 \text{ 94} \rightarrow 2 \text{ 95} \rightarrow \text{96}$ (86AJC579; 87AJC865; 86AJC1983; 83NJC345; 86ZOB863). These experiments, however, appear to be of a little importance because they usually lead to artificial products (89TL1383).

The conditions of the equilibrium between **95** and **96** ($X = \text{BF}_4, \text{ClO}_4$; R^1 to $R^5 = \text{H}$, alkyls, aryls) including their thermodynamic interpretation have been established, and the structures of the radicals **95** proved by spectroscopic—mainly ESR—experiments (86NJC345; 89BCJ2279; 89RCI57).

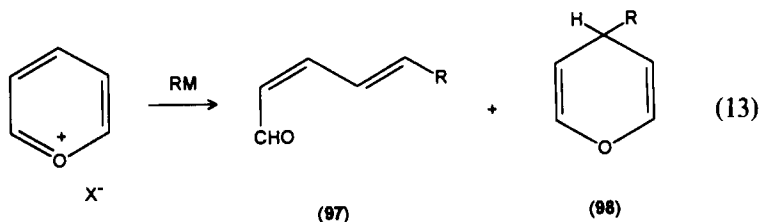
A new UV-photochemical method permitting the reduction of perchlorate **99a** to 2,6-diphenyl-4*H*-pyran by a hydride-like transfer from other 4-alkyl-2,6-diphenyl-4*H*-pyrans has been reported (93T3793).

2. Reactions with C-Nucleophiles

Conversion of pyrylium salts with organolithium and Grignard reagents to pyrans via reductive alkylation or arylation has been enriched by applications of organocopper and other organometallic compounds as well as by photochemical activation. Several new studies with anions of C-acids have been published as well.

a. *Organolithium Reagents.* The reactions of unsubstituted pyrylium perchlorate with MeLi, BuLi, sec-BuLi, *t*BuLi, BuC \equiv CLi, Ph, PhC \equiv C, and 2-thienyllithium in THF at -78°C gave only dienals **97**, whose prevailing (2*Z*,4*E*)-configurations confirm that unstable 2-*R*-2*H*-pyrans are the initial intermediates [85CC782; 89JCS(P1)683]. On the other hand, 15–25% of 4*H*-pyrans **98** ($R = \text{Ph}$, (*E*)-PhCH=CH, (*E*)-Bu₃SnCH=CH) were detected together with prevailing (2*Z*,4*E*)-dienals **97** after the reaction of pyrylium tetrafluoroborate with RLi in THF at -70°C ; see Eq.(13), where $M = \text{Li}$ and $X = \text{BF}_4$ (91S320). Moderate yields of the correspond-

ing 4*H*-pyrans **98** were obtained also with allyllithium and 1,3-dithian-2-ylolithium. A higher yield (41%) of **98** (R = PhCH₂) achieved from



PhCH₂Li has been explained by an exceptional cycloaddition mechanism [89JCS(P1)683].

2,6-Disubstituted pyrylium salts **99** exhibit a greater tendency to be converted to 4*H*-pyrans. Thus, organolithium reagents R'M (M = Li) were successfully used for the transformations of **99a** to **92** (R = Ph; R' = PhC≡C or Me₃SiC≡C) (82TL1747; 83JOC2757; 83S491) and **99b** to **92** (R = *t*Bu, R' = (CO)₃MnC₅H₄) in THF below -60°C or in ether (85KGS593). An earlier report that identified the structure as **100a** instead of the formula **92** (R = Ph; R' = PhC≡C) has been corrected (82TL1747). On the other hand, the conversions of **99a** in THF above 0°C were observed to lead either to dimerization of **100a** (82TL1747) or simply to the isomerization of **92** (R = Ph; R' = Me₃SiC≡C) to **100b** (83S491).

The reactions of dilithium reagent LiC≡CLi with salts **99** (X = ClO₄) in ether afforded the expected bis-4*H*-pyrans **101** in 34 and 23% yields, respectively (85LA708).

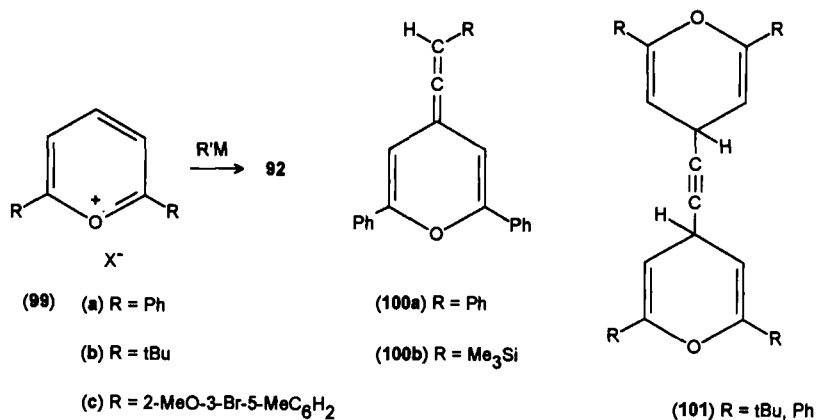
b. Grignard Reagents. Similar to the organolithiums, the organomagnesium reagents BuMgBr, *t*BuMgBr, and PhMgBr with pyrylium perchlorate gave only the corresponding dienones **97** (R = Bu, *t*Bu, Ph). However, mixtures of **97** and 4*H*-pyrans **98** (R = CH₂=CHCH₂, PhCH₂) were isolated and separated in the cases of CH₂=CHCH₂MgBr and

TABLE XI
SOME YIELDS OF DIENALS **97** AND 4*H*-PYRANS **98** OBTAINED ACCORDING TO
EQ. (13) WITH VARIOUS ORGANOMETALLIC REAGENTS^a

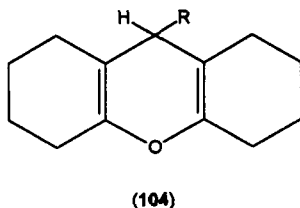
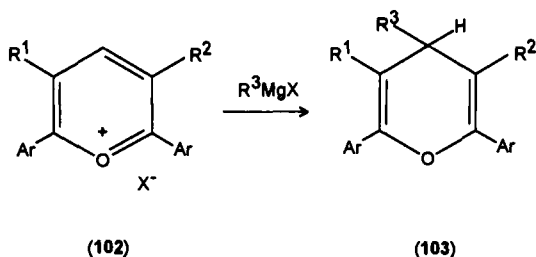
RM	97(%)	98(%)	RM	97(%)	98(%)
CH ₂ =CHCH ₂ Li	24 ^b	6	PhCH ₂ Li	27	41
CH ₂ =CHCH ₂ MgBr	57	9	PhCH ₂ MgCl	26	26
(CH ₂ =CHCH ₂) ₂ CuMgBr	48	12	(PhCH ₂) ₂ CuLi	6	76

^a Reference 89JCS(P1)683.

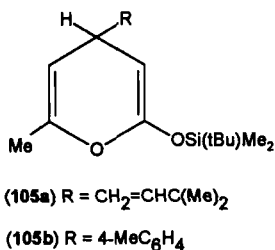
^b Mixture of stereoisomers.



PhCH_2MgCl [89JCS(P1)683]. On the other hand, 2,6-disubstituted pyrylium salts lacking substituents in position 4 afforded various 4*H*-pyrans, namely: **99a** + $\text{MeMgI} \rightarrow \mathbf{92b} + \mathbf{96}$ ($R^1 = R^5 = \text{Ph}$; $R^2 = R^3 = R^4 = \text{H}$) (93H869), **99a** + $\text{PhMgBr} \rightarrow \mathbf{92c}$ (90KGS603), **99b** + $\text{MeMgI} \rightarrow \mathbf{92}$ ($R = t\text{Bu}$, $R' = \text{Me}$) (85CB3700), **99b** + $t\text{BuMgBr} \rightarrow \mathbf{92}$ ($R = R' = t\text{Bu}$) + **92a** (87CCC1305), and **99c** + $\text{MeMgI} \rightarrow \mathbf{92}$ ($R = 2\text{-}$



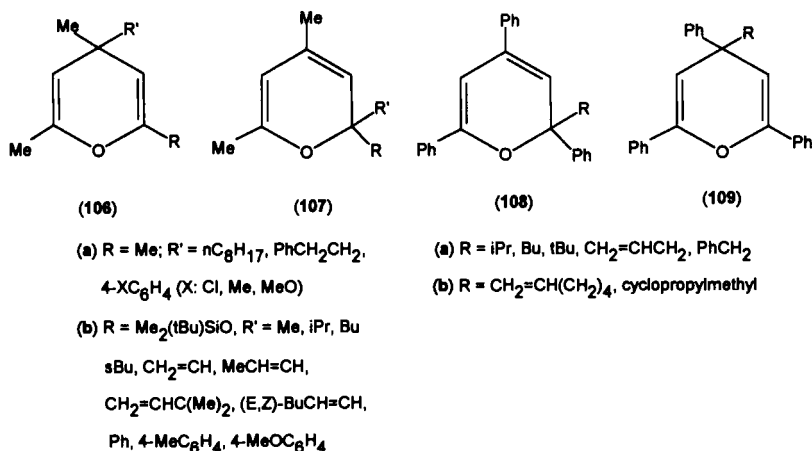
R : see text



MeO-3-Br-5-MeC₆H₂; R' = Me) (86TL3183; 88JOC374; 88PAC477). 2,3,6-Trisubstituted and 2,3,5,6-tetrasubstituted pyrylium salts **102a-c** reacted analogously, giving 4*H*-pyrans **103a-c** (86TL3183; 88JOC374; 88PAC477; 90KGS603). Fused 4*H*-pyran **104** (R = 2-thienyl) was obtained from the corresponding 4-unsubstituted pyrylium perchlorate with 2-thienylmagnesium bromide (91KGS900).

c. Organocopper Reagents. Organocuprates have been observed to attack pyrylium salts predominantly at position 4, as demonstrated in Table XI where the reactions of RLi, RMgX, and R₂CuLi(Mg)X with the same substrates are compared. In the case of Ph₂CuLi 63% of 4*H*-pyran **98** (R = Ph) was obtained whereas only stereoisomeric dienals **97** (R = Ph) were found with PhLi and PhMgBr [89JCS(P1)683].

Substituted pyrylium salts have usually afforded the corresponding 4*H*-pyrans. Thus, 71% of **105a** and 34% of **105b** were exclusively isolated after the reaction of corresponding 2,6-disubstituted pyrylium tetrafluoroborates with R₂CuLi (89JOC1931). Similar 2,4,6-trisubstituted salts have been converted primarily to 4*H*-pyrans **106** but partly to 2*H*-isomers **107**. Thus, 71–90% of mixtures of **106a** and **107a** containing 60–89% of 4*H*-isomers **106a** were obtained with R'Cu(I), R₂CuLi, or R₂CuMgBr in



Et₂O–THF at –78° to 0°C. Surprisingly, 2*H*-pyrans could not be isolated from the mixtures because of their kinetic lability toward the reagents (87H1495). On the other hand, no such difficulties were found in more extensive attempts to prepare and separate mixtures of isomers **106b** and **107b** (87TL6305; 89JOC1931). With Me₂CuLi (in THF–Et₂O) or Bu₂CuLi (in THF–Et₂O–hexane), only 4*H*-pyrans **106b** were isolated in 28–65%

yields; but unexpectedly, Me_2CuLi in Et_2O gave 50% of pure 2*H*-pyran **107b** ($\text{R} = \text{Me}$). In general, $\text{R}'_2\text{CuLi}$ reagents have been recognized to give higher yields of products than $\text{R}'_2\text{CuMgX}$ (89JOC1931).

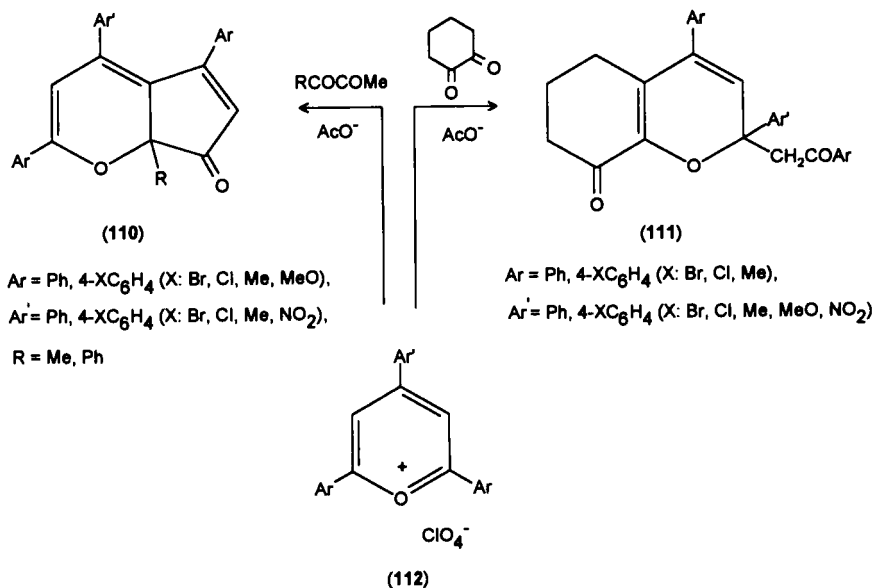
d. Other Organometallic Reagents. The organometallics Ph_4Ti and Ph_4Zr were found to react with pyrylium perchlorate to give mixtures of stereoisomeric dienals like **97** ($\text{R} = \text{Ph}$) in 75 and 24% yields, respectively [89JCS(P1)683]. On the other hand, the UV photolysis of Bu_4Sn , Bu_4Ge , and Bu_4Si ($\lambda > 400 \text{ nm}$) in the presence of 2,4,6-triphenylpyrylium tetrafluoroborate in acetonitrile gave mixtures of pyrans **108a** ($\text{R} = \text{Bu}$) and **109a** ($\text{R} = \text{Bu}$) in which the 2*H*-isomer **108a** predominated; the conversions strongly depended on strengths of the carbon-metal bonds ($\text{Bu}_4\text{Sn} > \text{Bu}_4\text{Ge} \gg \text{Bu}_4\text{Si}$). The relative reactivities of various alkyls (R , R') toward the substrate salt were in the order $\text{PhCH}_2 > \text{CH}_2=\text{CHCH}_2 > t\text{Bu}$, $i\text{Pr} > \text{Bu}$ $\text{Me} >$ using $\text{R}_2\text{SnR}'_2$ reagents. Other organometallics $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_4\text{M}$ ($\text{M} = \text{Sn}$, Ge) gave mixtures of **108b** and **109b** with 2*H*-isomers **108b** prevailing. A mechanism involving an initial electronic excitation of the starting pyrylium ions has been proposed (90CL2191).

e. Anions of C-Acids. The reactions of substituted pyrylium salts with two major types of C-nucleophiles have been investigated, namely with various enolates and C-salts of diazo compounds.

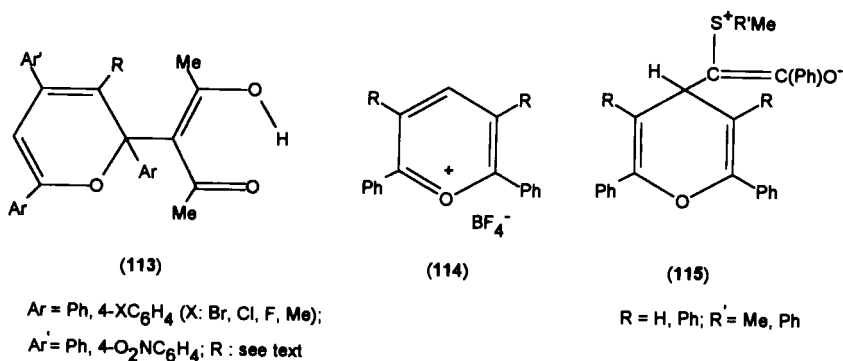
Remarkable ring-opening-ring-closing transformations of 2,4,6-triarylpyrylium perchlorates **112**, involving initial C-nucleophilic attacks at position 2 of the ions to yield fused 2*H*-pyrans **110** (31–52%) or **111** (41–76%), have been recognized in the reactions with α -diketones and acetate-like catalysts (88ZC295; 89JPR306); see Scheme 6. Detailed mechanisms have been discussed (89JPR293; 89JPR306).

In contrast to the above-mentioned behavior of α -diketones, β -dicarbonyl reagents reacted with 2,3,4,6-tetrasubstituted pyrylium perchlorates to give 2*H*-pyrans **113** ($\text{R} = \text{Me}$, Et). If the substituent R in the starting salt was lacking, heterocycle **113** ($\text{R} = \text{H}$) was unstable and underwent a spontaneous ring opening to its valence isomer. Hence the earlier report (81ZOR1050) of the preparation of **113** ($\text{R} = \text{H}$) should be corrected (81ZC446; 86JPR359). Unlike the diketones, thionium betaines $\text{MeS}^+(\text{R}')\text{CH}=\text{C}(\text{Ph})\text{O}^-$ have been reported to attack position 4 of tetrafluoroborates **114**, affording 4*H*-pyrans **115** (81CL1535).

Lithiodiazo compounds or analogous by deprotonated species have been observed to be considerably reactive toward pyrylium salts. Thus, 4*H*-pyrans **116a–d** were prepared from 2,6-disubstituted 4-methylpyrylium tetrafluoroborates and diazo derivatives $\text{N}_2\text{CH}_2\text{COR}'$ either after their



SCHEME 6



reaction ($\text{R}' = \text{EtO}$) with BuLi (THF- Et_2O , -78°C) to Li salts (83TL5355; 85CB3700; 85S569) or after their deprotonation ($\text{R}' = \text{Ph}$, EtO) with Et_3N in CHCl_3 at low temperature (85S569). Sometimes, only artifacts from unstable 2H-pyrans were isolated (85CB3700; 87JOC3851).

A number of phosphorus-containing 4H-pyrans of type 117 were prepared analogously in variable yields using activation procedures with BuLi (83TL5355; 85CB3700; 87JOC3851) or Et_3N (84CB2233; 85S569) (Table XII). In some cases, pyrans were not obtained, whereas in others, only

TABLE XII
 2,4,4,6-TETRASUBSTITUTED 4*H*-PYRANS 117

R ¹	R ²	R ³	R ⁴	R ⁵	Reagent ^a	Yield (%)
Me	Me	MeO	MeO	Me	A	22 ^b
<i>t</i> Bu	H	<i>t</i> Bu	<i>t</i> Bu	<i>t</i> Bu	B	50 ^{c,d}
<i>t</i> Bu	H	MeO	MeO	<i>t</i> Bu	B	40 ^d
<i>t</i> Bu	H	EtO	EtO	<i>t</i> Bu	B	36 ^d
<i>t</i> Bu	H	Ph	Ph	<i>t</i> Bu	B	70 ^{c,d}
<i>t</i> Bu	Me	MeO	MeO	<i>t</i> Bu	A	73 ^e
<i>t</i> Bu	Me	MeO	Ph	<i>t</i> Bu	A	58 ^e
<i>t</i> Bu	Me	Ph	Ph	<i>t</i> Bu	A	43 ^e
<i>c</i> -C ₃ H ₅	H	Ph	Ph	<i>c</i> -C ₃ H ₅	B	50 ^d
1-Me- <i>c</i> -C ₃ H ₄	H	Ph	Ph	1-Me- <i>c</i> -C ₃ H ₄	B	60 ^d
Ph	H	Ph	Ph	Ph	B	35 ^d
Ph	Me	MeO	MeO	Ph	A	18 ^b
4-MeC ₆ H ₄	H	Ph	Ph	4-MeC ₆ H ₄	B	60 ^d
4-MeOC ₆ H ₄	H	Ph	Ph	4-MeOC ₆ H ₄	B	70 ^d
4-FC ₆ H ₄	H	Ph	Ph	4-FC ₆ H ₄	B	15 ^d
4-ClC ₆ H ₄	H	Ph	Ph	4-ClC ₆ H ₄	B	20 ^d

^a **A**: Li(CN₂)P(O)R³R⁴; **B**: Et₃N + N₂CHP(O)R³R⁴; see text.

^b Reference 87JOC3851.

^c Reference 85S569.

^d Reference 84CB2233.

^e References 83TL5355 and 85CB3700.

mixtures with 100-like by-products resulted. The reasons for these findings have been discussed in terms of possible reaction mechanisms (84CB2233).

The addition of deprotonated nitromethane (with Et₃N) to perchlorate **99b** was found to proceed in at least two steps, affording bis-4*H*-pyran **118** (R = *t*Bu) as the final product. Analogous reaction of **99b** with alkali cyanide gave no pyrans (87CCC1305).



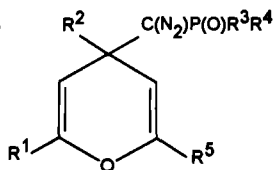
(116)

(a) R = Me, R' = EtO

(b) R = *t*Bu, R' = EtO

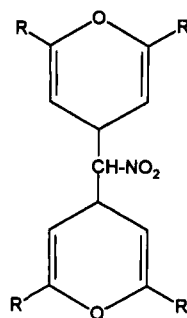
(c) R = *t*Bu, R' = Ph

(d) R = Ph, R' = EtO



(117)

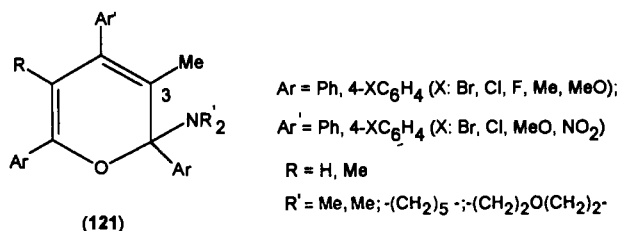
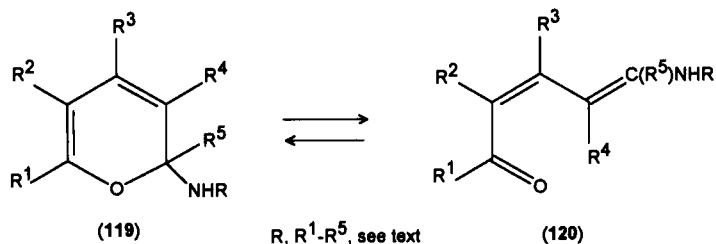
R¹ to R⁵, see text



(118)

3. Reactions with *N*-Nucleophiles

Literature data have been reviewed (82UK817). Sufficient progress has been achieved regarding mechanisms of the reactions of pyrylium salts **94** with ammonia and primary amines RNH_2 leading to the corresponding pyridinium salts as final products [81JCS(P2)571; 82JCS(P1)117; 83JOC5268; 84JCS(P2)849; 84JCS(P2)857; 85JCS(P2)171]. The first intermediates formed are *N*-protonated 2-amino-2*H*-pyrans whose deprotonation to the labile parent heterocycles **119** initiates subsequent reaction steps via the valence-isomeric aminodienals or -dienones **120**. In the case of secondary amines the reaction path usually stops at the dienone stage (81ZC282; 83JOC5268; 84JPR657). The equilibrium between **119** and **120**

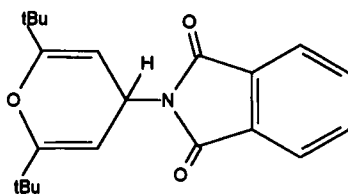
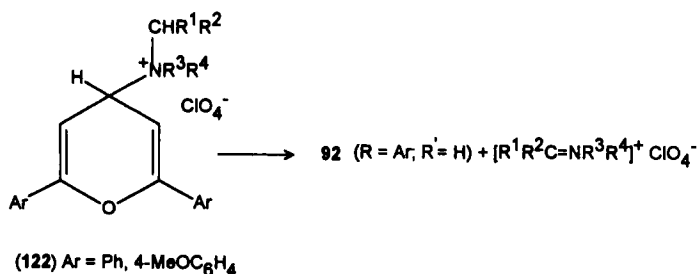


is mainly controlled by relative intramolecular repulsions of substituents within both valence isomers, as concluded from spectroscopic investigations [81CS256; 82JCS(P1)117; 83JOC5268; 84JCS(P2)849; 85JCS(P2)171].

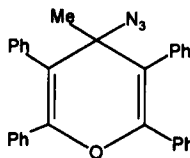
Only one case has been reported [84JCS(P2)849] of isolable 2*H*-pyrans arising from a primary amine, namely, **119** ($\text{R}^1 = \text{R}^5 = 4\text{-HO}_3\text{SC}_6\text{H}_4$; $\text{R}^2 = \text{R}^4 = \text{H}$; $\text{R}^3 = 3\text{-HO}_3\text{S}-4\text{-MeOC}_6\text{H}_4$; R = sec-Bu). On the other hand, a number of substituted 2-amino-2*H*-pyrans **121** were successfully prepared with secondary amines $\text{R}'_2\text{NH}$ (81ZC282; 82GEP155900; 84JPR657). Undoubtedly, **120**-like open forms are destabilized by the 3-methyl group (R^4) repulsively interacting with the carbonyl group; hence the products **121** may be isolated.

An unexpected reduction of 2,6-diarylpyrylium perchlorates **99**

(R = Ph, 4-MeOC₆H₄) to corresponding 4*H*-pyrans **92** (R = Ph, 4-MeOC₆H₄; R' = H) was observed with some tertiary amines R¹R²CHNR³R⁴ (R¹, R², R³, R⁴ = H, Me, Et, Et; Me, Me, Et, *i*Pr; H, H, C₆H₁₁, C₆H₁₁). A possible mechanism involving intermediates **122** has been proposed (81JHC1235).



(123)



(124)

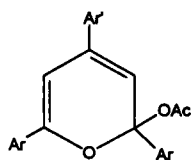
A novel example of the addition of phthalimide ion to **99b** affording 4*H*-pyran **123** was described (87CCC1305).

Like the 2-amino-2*H*-pyrans, analogous 2-azido-2*H*-pyrans have been observed to be unstable intermediates in the known synthesis of oxazine derivatives from pyrylium salts and NaN₃; see Section V.G.3. Only some sterically hindered pyrylium cations can generate the intermediates, and attempts have been made to rationalize these observations by quantum-chemical approaches (84T3539; 84T3549). Exceptionally, 4-azido-4*H*-pyran **124** was isolated after the reaction of 4-methyl-2,3,5,6-tetraphenylpyrylium perchlorate with NaN₃ (84T3539).

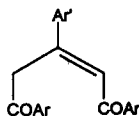
4. Reactions with *O*-Nucleophiles

Water covalently interacts only with strongly electrophilic 2,4,6-triarylpyrylium perchlorates (possessing substituents like SO₃H and CO₂H) in the aryl group to equilibrate with the corresponding 2-hydroxy-

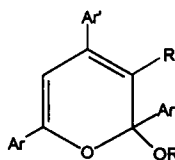
2*H*-pyrans (pseudobases). The mechanism and substituent effects are discussed on the basis of kinetic data [84JCS(P2)841; 84JCS(P2)857; 84JCS(P2)867]. The most popular objects for kinetic and equilibrium studies in terms of chemical thermodynamics have been, however, interactions of different 2,4,6-trisubstituted pyrylium salts with variously generated MeO^- ions [82JOC960; 86JCS(P2)271; 86JOC4385; 87JCS(P2)1427; 88JOC1729; 89JCS(P2)1393]. Although the results appear to be of little preparative importance, because of the lability of 2,4,6-trisubstituted 2-methoxy-2*H*-pyrans and 4-methoxy-4*H*-pyrans, at least two conclusions seem to be of general interest: (i) 4*H*-Isomers are usually products of kinetic control while 2*H*-isomers are, as a rule, thermodynamically more stable; (ii) the ring opening of the 2*H*-pyrans to their valence isomers is usually slower than their formation [86JCS(P2)271; 86JOC4385; 88JOC1729]. Some discrepancies in the findings with a quantum-chemical interpretation have also been mentioned (86JOC4385). The lability of 2,4,6-triaryl-2-methoxy-2*H*-pyrans was exploited in methods for the replacement of counterions in corresponding pyrylium salts (89SUP1447824).



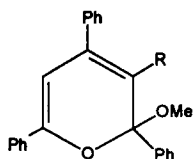
(125) Ar, Ar' = see text



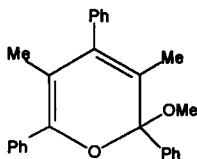
(126)



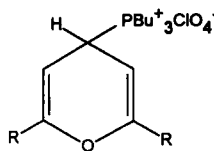
(127) (a) Ar = Ph, 4- XC_6H_4
(X: Br, Cl, Me, NO_2),
Ar' = Ph, 4- XC_6H_4
(X: Br, Cl, Me, O_2N), R = Me
(b) Ar = Ar' = Ph, R = Et



(128) R, see text



(129)

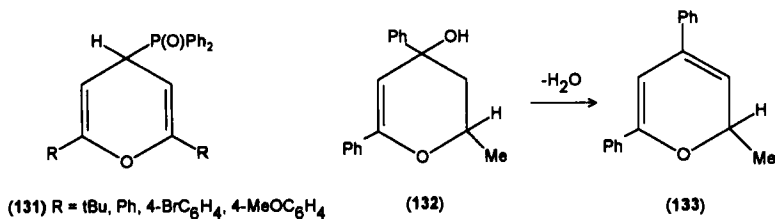
(130) R = tBu, Ph, 4- FC_6H_4 , 4-MeOC $_6\text{H}_4$

Acetate ions reversibly add to 2,4,6-triarylpyrylium perchlorates to form 2-acetoxy-2*H*-pyrans **125**, as found for the case Ar = Ar' = Ph in a dry Et_3N -AcOH mixture (83JCS(P1)497]; but with AcONa - H_2O diketones **126** were the only products (84JPR287; 85JPR529).

2,3,4,6-Tetrasubstituted and 2,3,4,5,6-pentasubstituted pyrylium perchlorates with sodium alkoxides or with Et_3N -alcohol mixtures were found to afford isolable 2-alkoxy-2*H*-pyrans **127a**, **127b**, **128** ($\text{R} = \text{Ph}$, PhCH_2), and **129** (81ZC260; 82GEP155899; 83JPR729), evidently due to the same substituent effects as in the case of **121**. 2-Methoxy derivative **127a** ($\text{Ar} = \text{Ar}' = \text{Ph}$) was also obtained by a methoxy-group transfer from an analogous thiopyran (83ZC333; 86JPR373), thereby showing the higher electrophilicity of pyrylium in comparison to similar thiopyrylium salts.

5. Reactions of *P*-Nucleophiles

The additions of phosphines to 2,6-disubstituted pyrylium perchlorates **99** have been enriched by a novel preparation of 4*H*-pyran-4-yl phosphonium salts **130** with Bu_3P in pyridine or acetonitrile (81JHC1235; 85JHC1179). A novel *P*-nucleophile generated *in situ* ($\text{Ph}_2\text{POMe} + \text{NaI} \rightarrow \text{Ph}_2\text{PONa} + \text{MeI}$) added to pyrylium salts gives 4*H*-pyrans **131** (90ZOB1012).

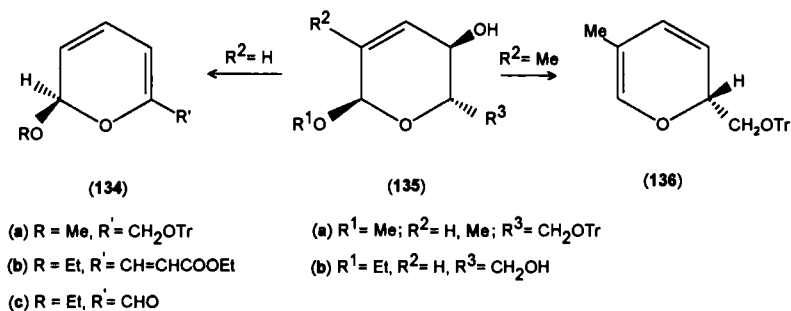


B. FROM DIHYDROPYRANS

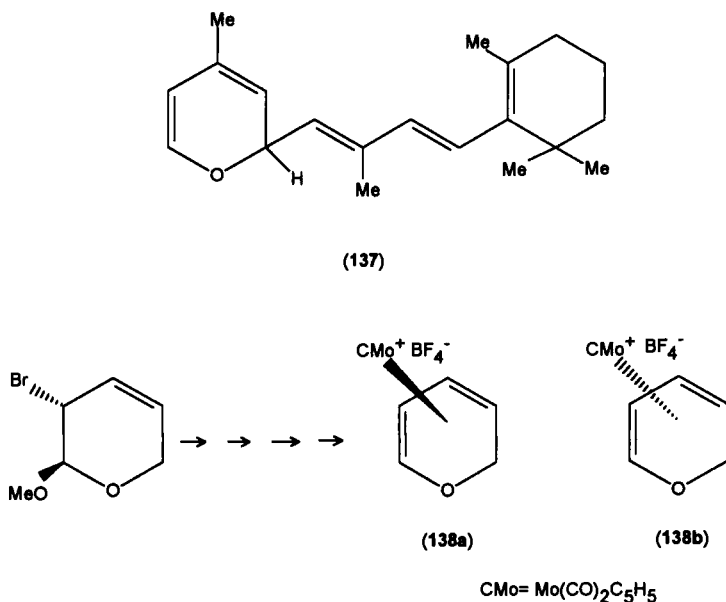
No conversions of tetrahydropyrans to pyrans have been reported in the last decade.

1. Preparation of 2*H*-Pyrans

Dehydration of 4-hydroxydihydropyran **132** smoothly gave 2*H*-pyran **133** by heating with silica gel in toluene [87JCS(P1)2125]. Unsaturated monosaccharide derivatives **135** were found to be transformed to optically active 2*H*-pyrans, namely: **135a** \rightarrow **134a** with $\text{MeMgI} \cdot (\text{Ph}_3\text{P})_2\text{NiCl}_2$, **135a** \rightarrow **136** with $\text{MeCu(I)} \cdot \text{BF}_3$ (87BCJ1441), and **135b** \rightarrow **134c** \rightarrow **134b** by subsequent reactions with $\text{Me}_2\text{SO}-(\text{COCl})_2$ and $\text{Ph}_3\text{PCHCO}_2\text{Et}$ reagents (93SY557). Compound **136** was only one of three reaction products



(87BCJ1441). A small amount of 3-acetoxy-2-acetoxymethyl-2*H*-pyran was obtained analogously from an unsaturated trisacetoxy monosaccharide derivative (85CCA321). Terpenoid 2*H*-pyran **137** was prepared from an appropriate 6-hydroxy-3,6-dihydro precursor with pyridinium chloride in DMF at room temperature (91TL4499). In the case of another 2-hydroxy-5,6-dihydropyran precursor, the corresponding 2*H*-pyran was too unstable to be isolated (90BCJ1611).

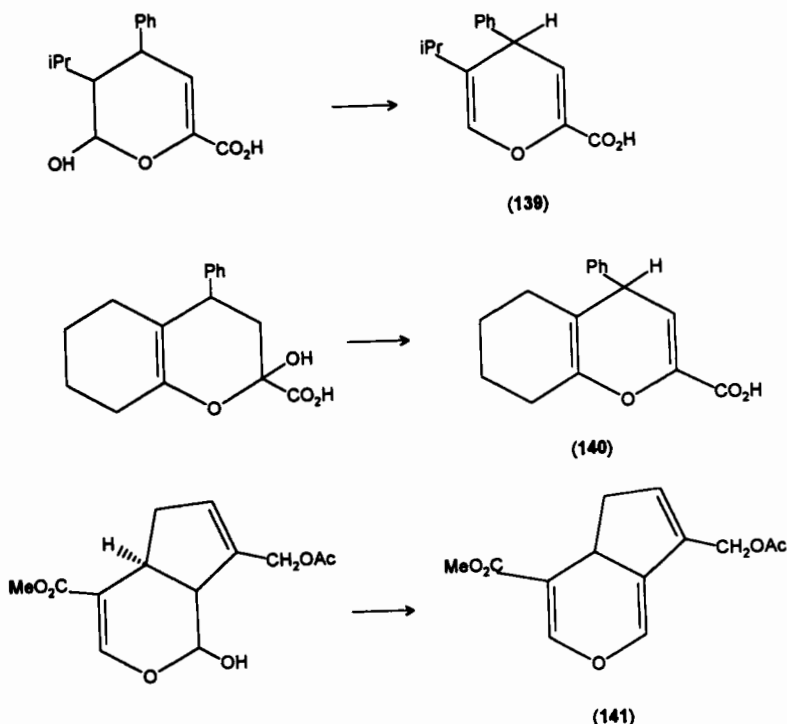


A new way to obtain Mo-coordinated parent 2*H*-pyran (**1**) has been discovered in a multistep procedure starting from D-arabinose via optically pure *trans*-5-bromo-6-methoxy-5,6-dihydro-2*H*-pyran, which gave (1*S*)-tetrafluoroborate **138a** by subsequent action of $\text{Mo}(\text{MeCN})_3\text{CO}$ and other reagents. The corresponding (1*R*)-enantiomer **138b** was obtained analo-

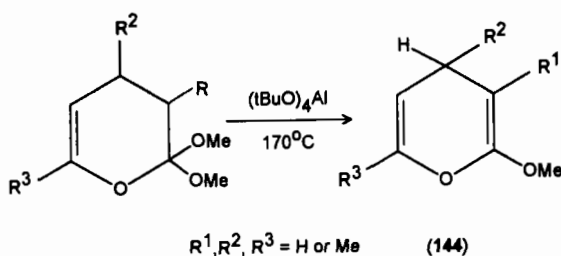
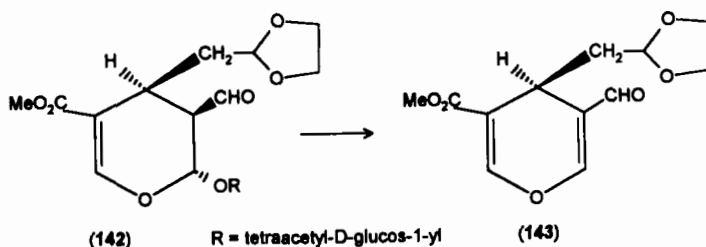
gously from L-arabinose (90JA9660). These procedures have been further elaborated for 2- and 2,6-substituted 2*H*-pyranyl ligands (93JA891).

2. Preparation of 4*H*-Pyrans

Two examples of dehydration procedures leading to 4*H*-pyran-2-carboxylic acids, namely **139** (85AP648) and **140** (86AP704), were performed by heating with TsOH in toluene. On the other hand, 4*H*-pyran **141** could be dehydrated only via the corresponding thio ester at elevated temperature (92CL139). Glycosidic derivative **142** was observed to decompose to optically active 4*H*-pyran **143** and tetraacetyl-D-glucose by chromatography on silica gel or with acidic and basic agents (81AG1005; 86LA1413).

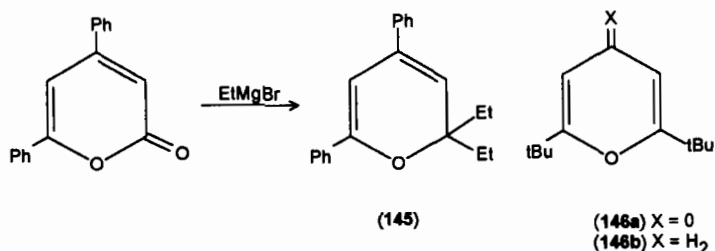


Novel successful conversions of cyclic ortho-esters to 2-methoxy-2*H*-pyrans **144** ($R^1, R^2, R^3 = H, H, H$; Me, H, H ; H, Me, H ; H, H, Me ; Me, Me, H ; Me, H, Me) by catalytic MeOH elimination were accomplished (83JOC2736).



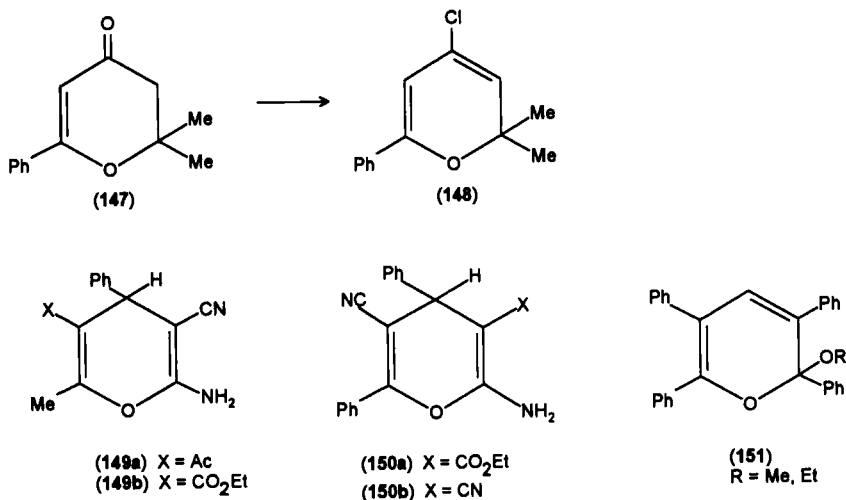
C. FROM PYRONES AND DIHYDROPYRONES

Little attention has been devoted to the synthesis of pyrans from pyrones in the last decade. The preparation of 2*H*-pyran **145** from the corresponding 2-oxo derivative and EtMgBr has been reported [87JCS(P1)2125]. An interesting reduction of the C=O group in 4-pyrone **146a** with $(i\text{Bu})_2\text{AlH}$ affording 4*H*-pyran **146b** (88OM1122) has not yet been generalized. The synthesis of 2*H*-pyran derivative **38** from methyl 2-pyrone-5-carboxylate (84JA7143) is mentioned in Section III.B.1 (Scheme 2). Dihydro-4-pyrone **147** was almost quantitatively converted to 2-chloro-2*H*-pyran **148** with oxalyl chloride under DMF catalysis (91HCA27). Questionable 2*H*-pyrans obtained from dehydroacetic acid and naphthalene-1,8-diamine were patented (83EUP71197).



D. FROM OTHER PYRANS

The reversibility of the transformations shown by Eq.(7) in Section III.B.2 may be exploited to replace the fragments $R^1C=CR^2$ or $R^5C=CNH_2$ in corresponding 2-amino-4*H*-pyrans, as was realized in the formal substitutions **149a** + $AcCH_2CO_2Et \rightarrow$ **149b** + Ac_2CH_2 (87-JHC1677) and **150a** + $CH_2(CN)_2 \rightarrow$ **150b** + $NCCH_2CO_2Et$ (82M53). Analogously, fused 4*H*-pyrans **44** ($R^1 = CN$; $R^2 = 4-FC_6H_4$, 2-furyl; $R^3 = R^4 = Me$) were prepared either from corresponding thioamide **44** ($R^1 = CSNH_2$, $R^2 = 4-FC_6H_4$) with malononitrile (88ZOR460) or by heating the corresponding 4-aryl-2,6-diamino-3,5-dicyano-4*H*-thiopyrans with morpholine in benzene with elimination of $NCCH_2CSNH_2$ (89ZOR1331). 4*H*-Pyran-4-yl betaines **115** ($R = Ph$) were reported to give 2-alkoxy-2*H*-pyrans by heating with MeOH or EtOH. A possible mechanism was discussed (81CL1535).

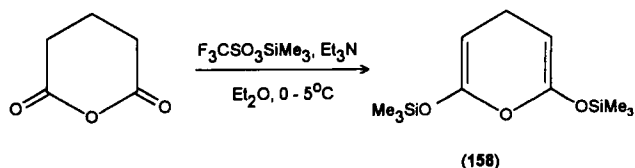
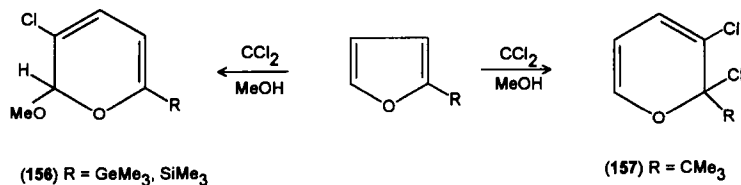
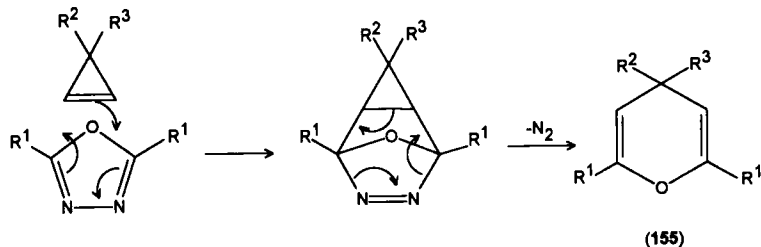
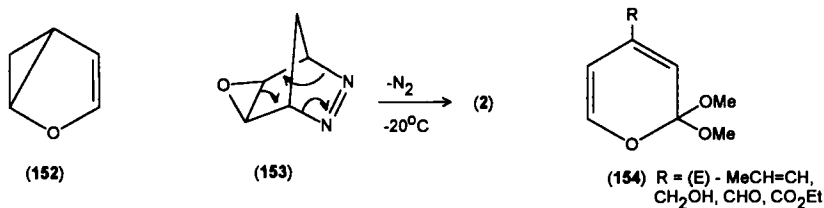


E. FROM OTHER HETEROCYCLES

Some oligoheterocyclic systems have been thought to be thermally transformable to pyrans. Thus, 2*H*-pyran (**1**) and/or its acyclic valence isomer have been considered as intermediates in a high-temperature thermolysis of **152** [87AG(E)1294]. On the other hand, 4*H*-pyran (**2**) was convincingly detected during spontaneous decomposition of bicyclic epoxy-diazene **153** (85CB5018). 2,2-Dimethoxy-2*H*-pyrans **154** were reported to be the final products of a flash vacuum pyrolysis (2×10^{-2} torr,

520–600°C) starting from more complex oligocyclic epoxides (81TL-4553; 81TL4557). A preparatively more interesting synthesis from 2,5-disubstituted 1,3,4-oxadiazoles and cyclopropenes led to 2,4,4,6-tetrasubstituted 4*H*-pyrans **155** (88TL3231).

2-Substituted furans were found to react with dichlorocarbene generated from a $\text{CHCl}_3\text{--NaOH--Et}_3\text{N}^+\text{CH}_2\text{PhCl}^-$ mixture in methanol to form either 2*H*-pyrans **156** (28–36%) or **157** depending on the π -donor–acceptor properties of the R-substituent (88JOM11). A versatile approach to 2,6-bis-trimethylsilyloxy-4*H*-pyran **158** was found from glutaric anhydride (87LA839). On the other hand, fused 4*H*-pyrans **11** ($\text{R} = \text{H}$; $\text{X} = \text{PhCH}$, 4-MeOC₆H₄CH) were detected by TLC after heating the corresponding 1-aryl-1,4-dihydropyridines with hydrochloric acid in dioxane (84KGS1393).



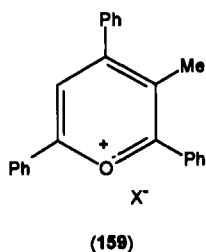
V. REACTIONS

A. AROMATIZATION AND OXIDATION

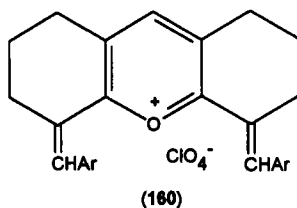
Investigations in the last decade have shown that aromatization of pyrans to pyrylium salts can sometimes be effected by oxidation depending on the structure of the starting oxygen heterocycle and the reagent.

1. Aromatizations of 2*H*-Pyrans

Most such conversions are nonoxidative. Thus, substituted 2-dimethylamino-4*H*-pyran **121** (Ar = Ar' = Ph, R = H, R' = Me) was easily converted to chloride **159a** with AcCl or PhCOCl and to iodide **159b** with MeI (84JPR657). Analogous 2-methoxy-2*H*-pyran **127** gave the same chloride **159a** with HCl or PhCOCl and the corresponding perchlorate **159c** with HClO₄ (83JPR729).



(a) X = Cl, (b) X = I, (c) X = ClO₄



Ar = Ph, 4-MeOC₆H₄, 2-furyl

2. Aromatizations of 4*H*-Pyrans

Two reviews are available in Russian (84KGS1011; 85UK1971). Unlike the 2*H*-pyrans mentioned above, 4*H*-pyran aromatizations may be oxidations and/or disproportionations depending on whether a hydride-like transfer from a substrate molecule proceeds to an oxidizing agent or to another substrate molecule. Some novel aromatizations of 4*H*-pyrans of general structure shown in Eq.(6) (Section III.B.2) to pyrylium salts **94** possessing the same substituents R¹ to R⁵ are summarized in Table XIII.

The aromatizations using HCl or HClO₄-Ac₂O reagents have also been applied to other fused 4*H*-pyrans **11** (X = ArCH), giving salts **160** (83ZOR2516). The procedures were successfully used for the conversion of 4*H*-pyran-crowns **161** to corresponding pyrylium-crowns **162** (88JOC374; 88PAC477).

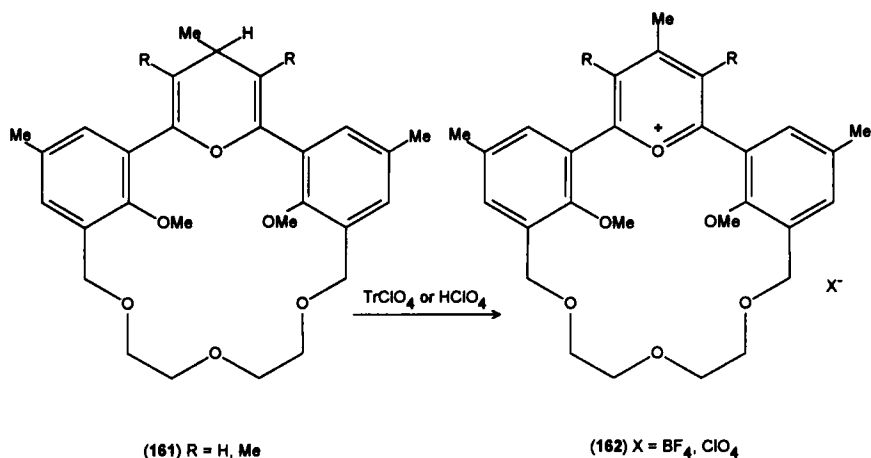
TABLE XIII
PYRYLIUM SALTS **94** PREPARED BY AROMATIZATIONS OF 4*H*-PYRANS

R ¹	R ²	R ³	R ⁴	R ⁵	X	Agent ^a	References
<i>t</i> Bu	H	H	H	<i>t</i> Bu	PF ₆	HPF ₆ , AcOH	88OM1122
<i>t</i> Bu	H	Me	H	<i>t</i> Bu	BF ₄	TrBF ₄	85CB3700
<i>t</i> Bu	H	C ₅ H ₃ MnL ₂ L' ₃ ^a	H	<i>t</i> Bu	ClO ₄	TrClO ₄	85KGS593
Ph	H	Me	H	Ph	BF ₄	TrBF ₄	87JOC3851
Ph	H	Me	H	Ph	BF ₄	TrBF ₄	93H869
Ph	H	Me	H	Ph	ClO ₄	FeCl ₃ , AcOH, HClO ₄	93H869
Ph	H	PhC≡C	H	Ph	ClO ₄	HClO ₄ , Ac ₂ O	82TL1747
Ph	H	C ₅ H ₃ MnL ₂ L' ₃ ^a	H	Ph	ClO ₄	TrClO ₄	85KGS593
Ph	Me	H	Me	Ph	ClO ₄	HClO ₄	90KF36
Ph	Me	Me	Me	Ph	BF ₄	O ₂ , BF ₃ · Et ₂ O ^b	90KF36
Ph	Me	Me	Me	Ph	ClO ₄	O ₂ , HClO ₄ , AcOH ^b	90KF36
Ph	Me	Ph	Me	Ph	BF ₄	O ₂ , BF ₃ · Et ₂ O	82NR83
Ph	Me	Ph	Me	Ph	ClO ₄	O ₂ , HClO ₄	82NR83
Ph	CHO	Ph	H	Ph	ClO ₄	TrClO ₄	89ZOR1342
Ph	CHO	Ph	H	Ph	ClO ₄	TrClO ₄ , MeNO ₂	90KGS603
—(CH ₂) ₄ —	H		—(CH ₂) ₄ —		ClO ₄	DTBQ, ^c HClO ₄	91KGS51
—(CH ₂) ₄ —	Ph		—(CH ₂) ₄ —		ClO ₄	DTBQ, ^c HClO ₄	91KGS51
—(CH ₂) ₄ —	4-MeOC ₆ H ₄		—(CH ₂) ₄ —		ClO ₄	DTBQ, ^c HClO ₄	91KGS51

^a Abbreviations: Tr = Ph₃C, L = CO, L' = Ph₃P.

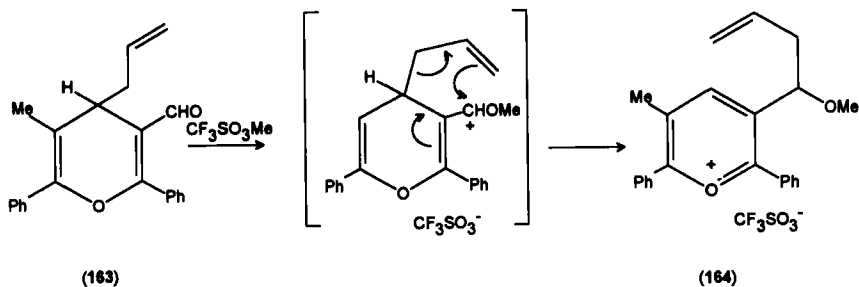
^b In addition to products of hydrolysis.

^c Di-*tert*-butylbenzoquinone.



In some cases, substituents were modified during the aromatizations. Thus, ligands were only partially replaced in 4*H*-pyrans **92** (R = *t*Bu, Ph; R' = (OC)₃MnC₅H₃) when they were aromatized with Tr⁺BF₄⁻ (Tr = Ph₃C) to appropriate 2,4,6-trisubstituted pyrylium tetrafluorobo-

rates. On the other hand, complete elimination of the 4-substituent leading to salts **99a,b** was observed with AcClO_4 (85KGS593) or with TrClO_4 from phosphorus *4H*-pyran **131** having $\text{R} = \text{Ph}$ (90ZOB1012). A similar scission of 4-aryl groups as radicals was discovered in the electrochemical oxidations of fused **104**-like *4H*-pyrans (91KGS900). An interesting 4-alkyl group migration in *4H*-pyran-3-carboxaldehyde **163** affording pyrylium salt **164** has been reported (90KGS603). Some successful preparations of pyrylium salts have also been performed in cases where *4H*-pyrans could not be isolated in a pure state (82NR83; 85KGS593; 93H869).



Aromatization procedures are evidently limited to alkylated and/or arylated *4H*-pyrans. Attempts to aromatize 2-amino-*4H*-pyrans **53** or their *N*-acetyl derivatives with Tr^+BF_4^- resulted in pyrone-like products (86JPR35); see the next section. A new UV-photochemical procedure for the aromatization of 4-alkyl-2,6-diphenyl-*4H*-pyrans with perchlorate **99a** has been reported (93T3793).

As far as the agents are concerned, the use of protic acids alone (HCl , HClO_4 , HBF_4 , HPF_6) seems to cause competitive disproportionation or hydrolysis of starting *4H*-pyrans (87H1495; 89ZOR1342; 90KF36). This suggestion is supported by the finding that 2,3,4,5,6-pentasubstituted *4H*-pyrans gave pyrylium salts only in the presence of O_2 while 2,4,6-, tri- and 2,3,5,6-tetrasubstituted starting compounds with acids in an inert atmosphere afforded only products of disproportionations (90KF36).

Fused *4H*-pyrans with more complex structures **55** were aromatized to corresponding pyridines lacking the 4-substituent with an $\text{AcONH}_4\text{--AcOH}$ reagent at elevated temperature (93JA872).

3. Conversion of 2-Amino-*4H*-pyrans to 2*H*-Pyridones, 2*H*-Pyrones, and Pyridines

3-Methyl-2,4,6-triphenylpyridine was obtained from 2-dimethylamino-*4H*-pyran **121** ($\text{Ar} = \text{Ar}' = \text{Ph}$, $\text{R} = \text{H}$, $\text{R}' = \text{Me}$) on heating with aqueous ammonia (84JPR657).

Some 3,4,5-trisubstituted and many 3,4,5,6-tetrasubstituted 2-amino-3-cyano-4*H*-pyrans **165** have been found to be oxidatively convertible into oxo-heterocycles **166a** and/or **166b** usually with ONOSO₃H–AcOH–H₂O mixtures at 0°C (86H1675; 89LA145) but sometimes with TrBF₄ in boiling benzene or with AlCl₃ in acetonitrile at 70°C (86JPR35); see Table XIV. The mechanisms of these conversions involving various ring-opening–ring-closing steps were proved to proceed via corresponding 3,4-dihydro derivatives (86H1675; 86JPR35; 89LA145); see Section V.C.5. Formation of some other **166a**-like pyridones from 4*H*-pyrans **165** with nonoxidizing H₂SO₄–EtOH mixtures at room temperature (86JPR35) might be explained by possible air oxidation of the 3,4-dihydro compounds.

Attempts to transform the 4*H*-pyrans **165** into the corresponding 1-aza analogs by heating with AcONH₄–AcOH mixtures resulted in the aromatization to 2-aminopyridines **167a** [R¹ = R² = Ph; R³ = Ph, 4-MeC₆H₄; X = H (86H1675)], **167b** [R¹ = Ph; R² = CN, CPh, CO₂Et;

TABLE XIV
OXIDATION OF 2-AMINO-3-CYANO-4*H*-PYRANS **165**

R ¹	R ²	R ³	Reagent ^a	Product yields (%)	
				166a	166b
H	CN	Ph	A	23	— ^b
Me	CN	<i>i</i> Pr	A	61	— ^b
Me	CO ₂ Et	Ph	A	43	12 ^b
Ph	Ph	Ph	A	—	81 ^c
Ph	Ph	4-MeC ₆ H ₄	A	—	76 ^c
Ph	Ph	4-MeOC ₆ H ₄	A	—	73 ^c
Ph	CN	<i>i</i> Pr	A	39	— ^b
Ph	CN	Ph	B, C	53	— ^d
Ph	CN	4-MeC ₆ H ₄	B	57	— ^d
Ph	CN	4-MeOC ₆ H ₄	B	51	— ^d
Ph	PhCO	Ph	A	17	34 ^c
Ph	PhCO	4-MeC ₆ H ₄	A	12	48 ^c
Ph	PhCO	4-MeOC ₆ H ₄	A	25	25 ^c
Ph	EtO ₂ C	<i>i</i> Pr	A	40	— ^b

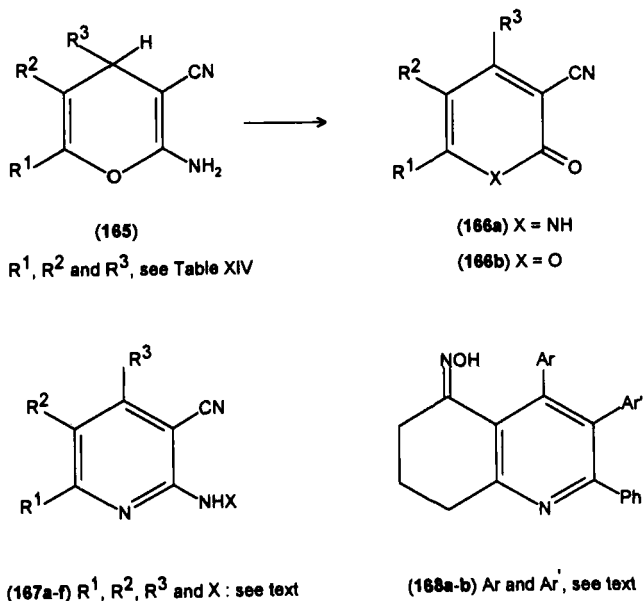
^a A: ONOSO₃H; B: TrBF₄; C: AlCl₃ (see text).

^b Reference 89LA145.

^c Reference 86H1675.

^d Reference 86JPR35.

$R^3 = \text{Me}$; $X = \text{H}$ (89LA145)], **167c** [$R^1 = \text{Me}$; $R^2 = \text{CONHPh}$; $R^3 = \text{Ph}$, $4\text{-ClC}_6\text{H}_4$, $4\text{-MeC}_6\text{H}_4$, $4\text{-MeOC}_6\text{H}_4$, $4\text{-O}_2\text{NC}_6\text{H}_4$; $X = \text{H}$ (89APR201)], and **167d** [$R^1 = \text{Me}$, $R^2 = \text{Ac}$, $R^3 = 2\text{-furyl}$, $X = \text{H}$ (90CCC718)]. Other *4H*-pyrans **165** formed mixtures of pyridines **167e** ($R^1 = \text{Me}$; $R^2 = \text{CO}_2\text{Et}$; $R^3 = 4\text{-ClC}_6\text{H}_4$, $4\text{-MeOC}_6\text{H}_4$, $X = \text{H}$) with corresponding 3,4-dihydro-2*H*-pyridones (91CCC2175). Conversions of **165** with PhNHNH_2 or

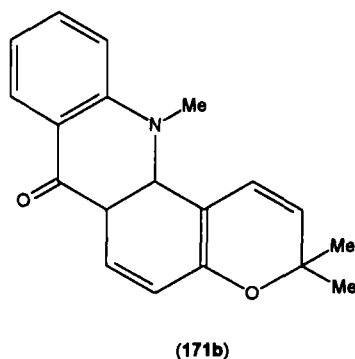
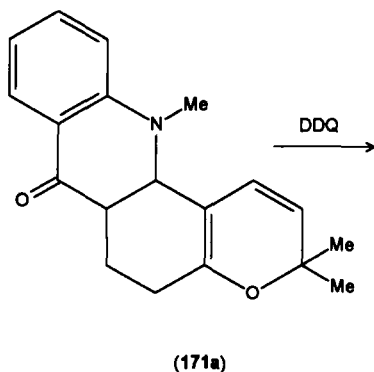
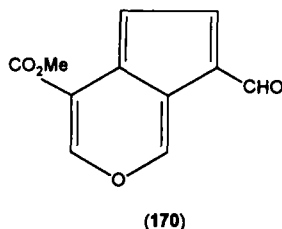
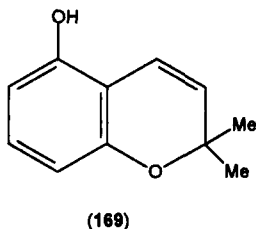


$\text{H}_2\text{NCSNHNH}_2$ to pyridines **167f** ($R^1 = \text{Me}$; $R^2 = \text{CO}_2\text{Et}$; $R^3 = 4\text{-ClC}_6\text{H}_4$, $4\text{-MeOC}_6\text{H}_4$; $X = \text{PhNH}$, $\text{H}_2\text{NCSNHNH}$) were also reported (89LA585). The appropriate reaction mechanisms have been discussed in detail (86H1675; 89LA145).

Mixtures of expected oximinopyridines **168a** ($\text{Ar} = 4\text{-MeOC}_6\text{H}_4$, $4\text{-O}_2\text{NC}_6\text{H}_4$; $\text{Ar}' = \text{H}$) and unexpected isomers **168b** ($\text{Ar} = \text{H}$; $\text{Ar}' = 4\text{-MeOC}_6\text{H}_4$, $4\text{-[O}_2\text{NC}_6\text{H}_4]$) were reported to be formed by aromatization of *4H*-pyrans **16** ($R^1 = \text{H}$, $R^2 = \text{Ar}$, $R^3 = \text{Ph}$) with hydroxylamine hydrochloride in EtOH (90KGS209). Complete decomposition of a hexasubstituted 2-amino-4*H*-pyran was also observed [90JCR(S)310]. The possibility of aromatizing 2-amino-4,6-diaryl-3-cyano-4*H*-pyrans with EtONa or PrONa to the corresponding 2-alkoxypyridines has been also discussed (88TL2703).

4. Dehydrogenation of Pyrans

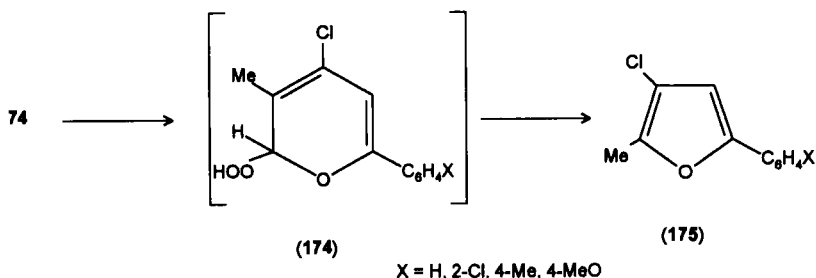
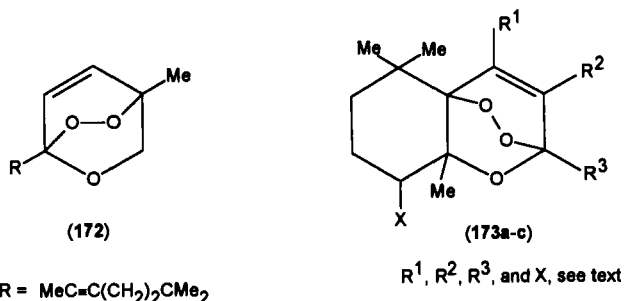
With DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) as the hydrogen-transfer agent in boiling benzene or toluene, conversions occur outside the pyran ring; e.g., **25** ($R^1 = \text{Me}$, $R^2 = R^3 = R^4 = \text{H}$) \rightarrow **169** (87JOC1972), **141** \rightarrow **170** (92CL139), and **171a** \rightarrow **171b** (84JHC913).



5. Photooxygenations of 2H-Pyrans

Singlet dioxygen generated by illumination ($^3\text{O}_2 + h\nu \rightarrow ^1\text{O}_2$, Bengal rose) has been found to form *endo*-peroxides of considerable stability from various 2H-pyrans: namely, **172** was obtained from **84a** (84HCA815); and **173a** ($R^1 = \text{H}$, $R^2 = R^3 = \text{X} = \text{H}$), **173b** ($R^1 = R^2 = \text{X} = \text{H}$; $R^3 = \text{CH}_2\text{CH}(\text{OH})\text{Me}$ or $\text{CH}_2\text{CO}_2\text{Me}$), and **173c** ($R^1 = \text{H}$, $R^2 = \text{H}$ or Me ; $R^3 = \text{Me}$, $\text{X} = \text{HO}$) were formed from the corresponding fused 2H-pyrans **81a** (87JOC1972; 88JMC713; 89HCA943) and **81b** (85HCA192). The stereochemistry of the cycloadditions has also been investigated (85HCA192; 88JMC713).

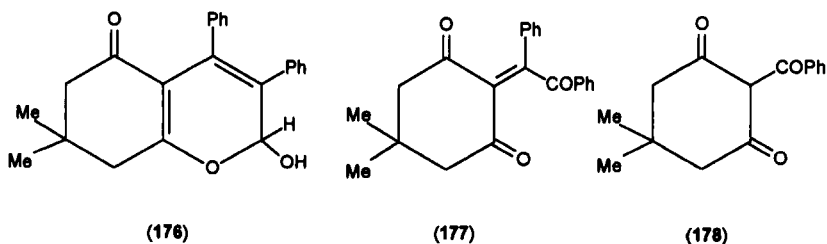
6-Substituted 4-chloro-3-methyl-2H-pyrans **74** were found to undergo photochemical oxidative ring contractions with O_2 to furans **175** (87KGS418; 90ZOR965). The reaction rates have been observed to depend

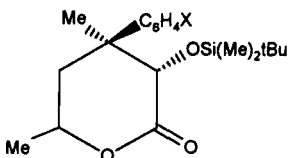


strongly upon the 6-substituents, and appropriate mechanisms involving peroxides **174** have been proposed on the basis of experiments with ^{18}O -labeled molecules (90ZOR965).

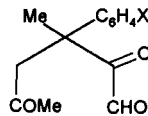
6. Other Oxidations of Pyrans

Oxidative decomposition of fused 2*H*-pyran **176** with $\text{Na}_2\text{Cr}_2\text{O}_7$ in AcOH led to triketones **177** and **178** (83H1013; 84BCJ734). The epoxidation agents MCPBA (*meta*-chloroperbenzoic acid) converted 2-trialkylsilyloxy-4*H*-pyran **106b** ($R' = 4\text{-MeC}_6\text{H}_4$) to a mixture of dihydropyrone **179** (33%) and dioxoaldehyde **180** (19%) in agreement with proposed mechanisms (87TL6305; 89JOC1931).





(179) X = 4-Me



(180) X = 4-Me

B. REDUCTION

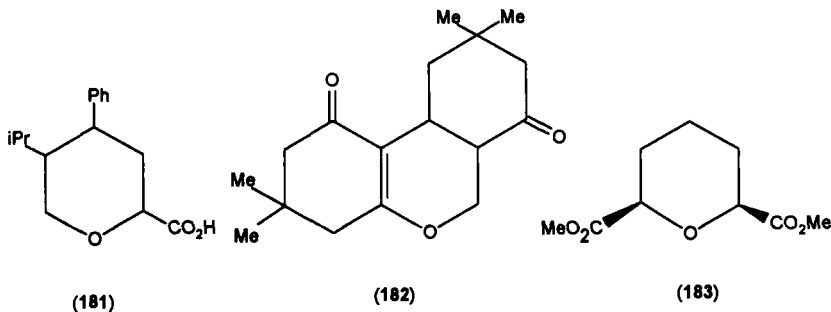
Partial and some total hydrogenations of 4*H*-pyrans have been accomplished in the last decade. Other reducing agents have been rarely used.

1. Hydrogenation of 4*H*-Pyrans

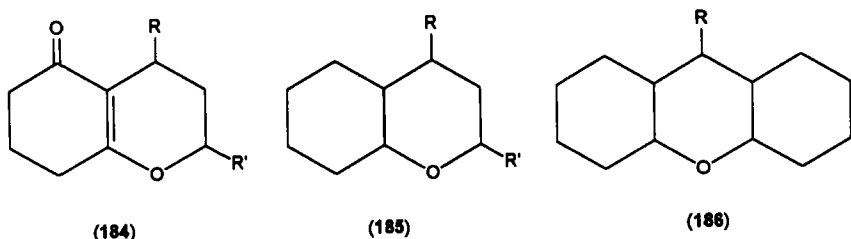
A review article covering catalytic hydrogenation of compounds containing a pyran ring is available in Russian (82NR62).

Palladium was used as a catalyst for the hydrogenation of 4*H*-pyran-2-carboxylic acid **139** to a diastereoisomeric mixture of tetrahydro derivatives **181** (86AP704) and fused diketone **22a** (R = Me, X = O) to dihydro derivatives **182** (83ZOR2027).

Rhodium-charcoal catalysts have been used more frequently for hydrogenations of monocyclic, bicyclic, and tricyclic 4*H*-pyran skeletons. Thus, dimethyl 4*H*-pyran-2,6-dicarboxylate gave exclusively *cis*-tetrahydro diester **183** (87CJC704). Mixtures of dihydro derivatives **184** (37–90%) and

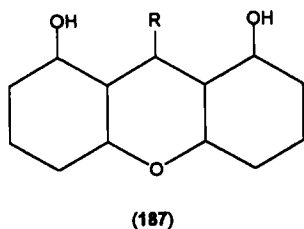


tetrahydro derivatives **185** (5–45%) were obtained from fused 4*H*-pyran ketones **16b** at 40–50°C (82ZOR2184). Somewhat less easily rationalized results were reported regarding the hydrogenation of fused 4*H*-pyrans **104** and analogous dioxo derivatives **54**, where tetrahydropyrans **186** (R = Et, Pr) were found to be the only products from **104** (R = Et, Pr) at 120°C whereas **186** (R = Ph) was obtained from diketone **54** (R¹ = R² = H,

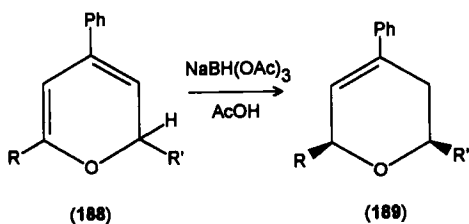


R, R' = Ph, Ph; 4-MeC₆H₄, Ph; Ph, 4-MeOC₆H₄;
4-MeOC₆H₄, 4-MeOC₆H₄

R, see text



R, see text



R, R' = Me, Me; iPr, iPr; Ph, Me

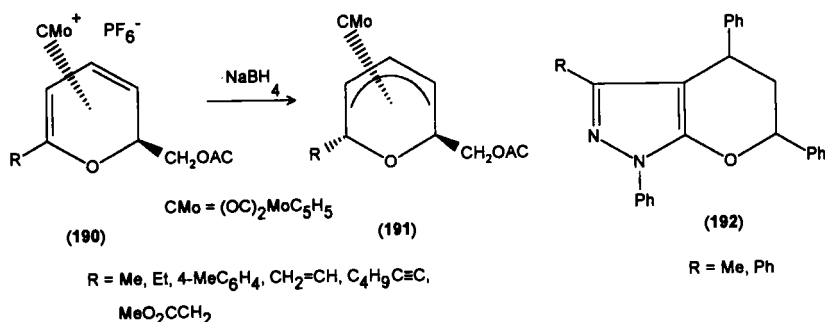
R³ = Ph) at 140°C. On the other hand, mixtures of **186** (R = H, Me) and dioles **187** were obtained from diketones **54** (R¹ = R² = H, R³ = H, Me) at 120–130°C. The hydrogenation of phenyl derivative **104** (R = Ph) gave **104** (R = *c*-C₆H₁₁) at 100°C and **186** (R = Ph) at 120°C. Similar results were achieved with a RuO₂ catalyst, which exhibited a rather higher activity (82NR62; 84ZOR1956).

2. Other Reductions of Pyrans

A modified borohydride reduction of 2*H*-pyrans **188** [NaBH₄ + 3 AcOH → NaBH(OAc)₃ + 3 H₂] yielded 80% of the corresponding *cis*-3,6-dihydro derivatives **189** (87TL1341). A reaction mechanism involving initial 3,6-addition of the reagent and reasons for its stereospecificity have been discussed in detail (88OPP231).

Standard borohydride reductions were successfully realized for pyranic ligand conversions in some optically active molybdenum-coordinated compounds. For example, hexafluorophosphate **190** (R = EtO) gave the corresponding neutral species **191** (R = EtO) in 94% yield. Analogous transformations were accomplished with other *R*-substituted salts **190** (93JA891).

In some cases, the 4*H*-pyran ring has been found to be inert toward NaBH_4 , affording only side-chain reduction products (89AP617). On the other hand, the hydride-like reagent $\text{Et}_3\text{SiH}-\text{CF}_3\text{CO}_2\text{H}$ was used for reduction of the 4*H*-pyran skeleton in fused pyrazolo derivatives **14** ($\text{R} = \text{H}$, Me ; $\text{R}' = \text{Ph}$), yielding diastereoisomeric products **192** (82KGS317).



C. ISOMERIZATION

A pyran ring can isomerize reversibly or irreversibly to open-chain or cyclic products. Both reaction paths have been investigated in the last decade.

1. Valence-Bond Tautomerism

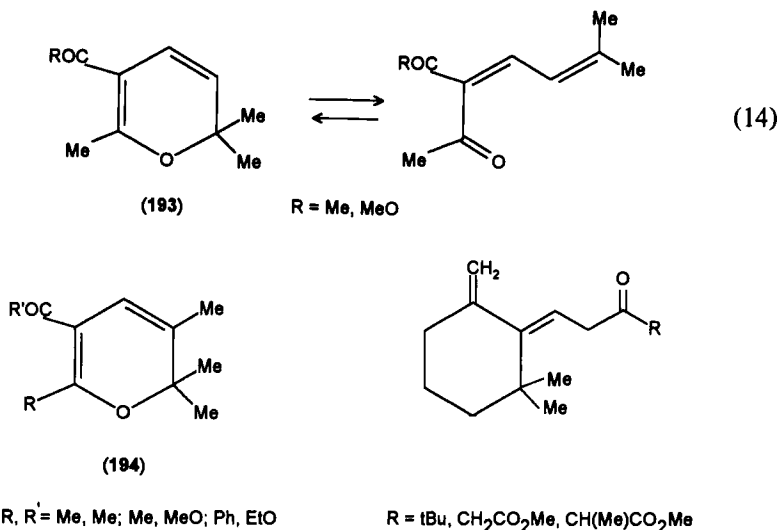
Progress regarding intramolecular and solvent effects on the electrocyclic process has been achieved.

a. *Tautomerism of Alkyl- and Aryl-Substituted 2*H*-Pyrans, Dienals, and Dienones.* This dynamic isomerism has been found to limit isolations and/or identifications of certain 2*H*-pyrans. As mentioned in Section III.D.1, 3-methoxycarbonyl-2*H*-pyran (**76**) could be obtained only as a substance containing traces of the valence tautomer **75** (92TL883). Equilibria (Eq. 14) containing 64% and 30% of cyclic forms **193** at 30°C were observed by ^{13}C NMR spectroscopy. Analogous 2*H*-pyrans **194** possessing the 3-methyl group contained only traces of open-chain tautomers under the conditions used (80IZV1011) as a consequence of typical destabilization of open-chain tautomers due to steric hindrance between the 3-methyl and other groups (especially the $\text{C}=\text{O}$ group).

Thermal equilibria of fused 2*H*-pyrans with their corresponding *cis*- β -ionone-like tautomers, e.g., between **81a** and **80a** ($\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^3 =$

Me, *t*Bu, CH₂CO₂Me, CH(Me)CO₂Me), were established (81TL1571; 83CL651; 83RTC302). The systems were found to be significantly solvent and temperature dependent. Thus, the extreme values of **81a**:**80a** (R³ = Me) ratios were determined as **91**:**9** (in Cl₂C=CCl₂ at 18–31°C) and **60**:**40** (in Cl₂C=CCl₂ at 113°C or in CDCN at 73°C) and the tautomerism was observed to be “frozen” below –50°C (81TL1571). On the other hand, terpenoic 2*H*-pyran **137** completely isomerized to its open-chain isomer on heating with a catalytic amount of pyridinium chloride in DMF (91TL4499).

Other 2*H*-pyrans **81a** were found to be photoisomerized to dienones **195** via valence-bond tautomers **80a** by prolonged UV illumination (λ = 254 nm) (83CL651; 83RTC302). The photochemical process started from excited singlet states, unlike the *Z* → *E* isomerization of β-ionone-type precursors **79a**, which proceeds via excited triplets (83RTC302).



b. *Tautomerism of 2-Dimethylamino-2*H*-pyrans and Dimethylamino-dienones.* One Russian research group has conducted many systematic investigations on the valence-bond tautomerism of the title compounds in connection with observed photochromic and solvatochromic effects (83JOC5268; 85IZV1075; 87IZV821; 88KGS1325; 89IZV1323; 90IZV2561). Solvent effects have been better recognized here than substituent effects. Polar and protic solvents generally were found to stabilize the open-chain dimethylamino tautomers. Thus, 2-dimethylamino-2*H*-pyrans **30** (R¹, R², R³ = Br, Me, Me; Br, MeO, MeO; EtO, MeO, Me;

EtO, EtO, Ph; NC, MeO, MeO) were present only in CCl_4 or $\text{Cl}_2\text{C}=\text{CCl}_2$ but were completely isomerized to the corresponding dienones **29** in CD_3OD or D_2O (89IZV1323). As shown in Table XV, the fractions of **30** ($\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{EtO}$, $\text{R}^3 = \text{Me}$) in equilibrium with **29** gradually decrease with the enhanced polarity of a given solvent (85IZV1075). In addition, a variable sensitivity of the equilibrium to solvent effects was observed for different substituents R^1 , as shown by the following: 2*H*-pyran tautomers **30**, for example, exhibited 16–73% (Cl), 75–89% (Br), 47–92% (EtO), and 88–97% (Me), increasing as the solvent changed from CHCl_3 to CH_3CN and then to CD_3OD (89IZV1323).

The same solvation effects were found to operate also in the tautomeric equilibria (15) and (16), where various solvents shifted the equilibria in parallel (85IZV1075; 89IZV1323). Surprisingly, equilibrium (15) was reported to be completely shifted to the right in the crystalline state (89IZV1323).

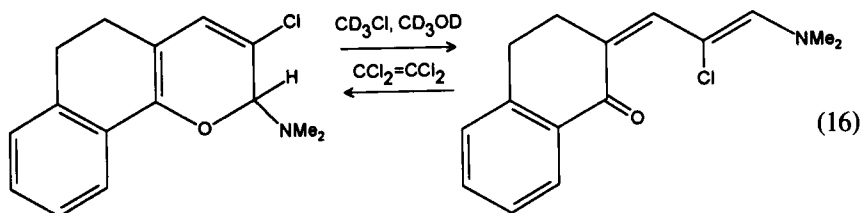
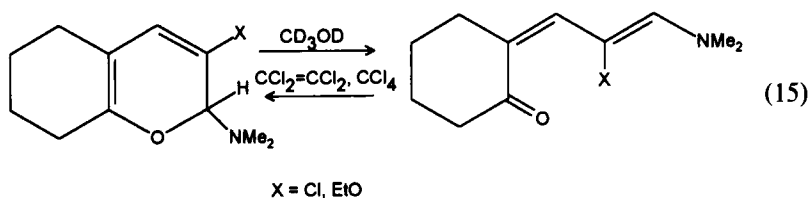


TABLE XV
CONTENTS OF 2*H*-PYRAN **30** ($\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{OEt}$, $\text{R}^3 = \text{Me}$) IN
EQUILIBRIUM MIXTURES WITH ISOMERIC DIENONE **29**
(85IZV1075)^a

Solvent	30 (%)	Solvent	30 (%)	Solvent	30 (%)
CCl_4	99	CDCl_3	67	CD_3CN	28
$\text{Cl}_2\text{C}=\text{CCl}_2$	98.5	CD_2Cl_2	58	CD_3OD	14
C_6H_6	88	$(\text{CD}_3)_2\text{CO}$	46	D_2O	0 ^b

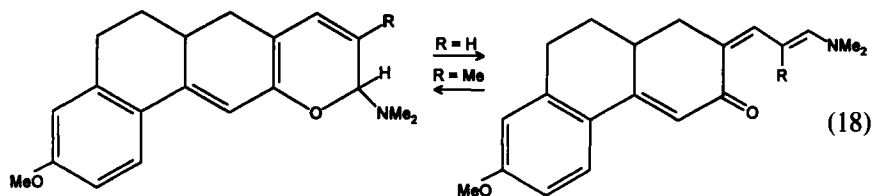
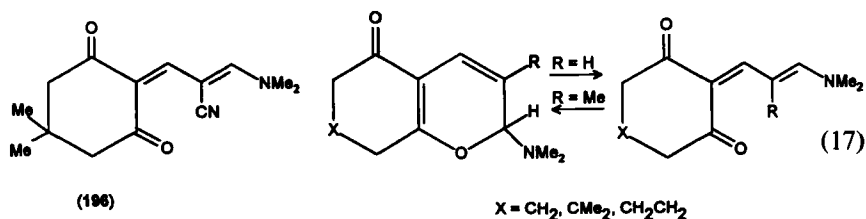
^a Determined by UV spectrophotometry.

^b Also in crystalline phase.

Substitution patterns differently influenced relative stabilities of both tautomeric forms. The correct interpretation is complicated because knowledge of the conformational behavior of differently substituted open-chain tautomers is limited. Stability factors recognized for 2-dimethylamino-2*H*-pyrans might be similar to those for appropriate alkyl and aryl derivatives: that is, (i) the presence of a sufficiently bulky substituent at position 3 (and maybe other vicinal substituents), (ii), a π -electron-withdrawing group at position 5, and (iii) no annulation of the pyran ring having less than a 6-membered atomic ring.

Interplay of all the favorable factors evidently caused some fused 3-substituted 2-dimethylamino-2*H*-pyran 5-ketones **31** ($R = \text{Cl, Me, } i\text{Pr, EtO, Me}_2\text{N}$) to exhibit no tautomerism at usual temperatures (85IZV1075; 87IZV821; 88KGS1325; 89IZV1323). The 3-substituent should not be, however, a strongly π -electron-withdrawing group, as indicated from the unexpectedly stable dimethylaminodienone **196** which gave no appropriate 3-cyano-2*H*-pyran tautomer **31** (89IZV1323).

The stability effects formulated above with condition (i) can be illustrated by the reverse shifts in equilibria (17) and (18) for $R = \text{H}$ or Me , respectively (87IZV821). The importance of condition (ii) is seen, for example, on comparing stabilities of the 5-ketonic 2*H*-pyrans **31** ($R = \text{Cl, EtO}$) with those lacking the $\text{C}=\text{O}$ group at position 5. Finally, condition (iii) seems to be in agreement with the findings that all attempts to prepare 5,6-annulated 2-dimethylamino-2*H*-pyrans with 5-membered carbo- or heterocyclic rings resulted exclusively in the formation of the corresponding open-chain tautomers (85IZV1075; 87IZV821).



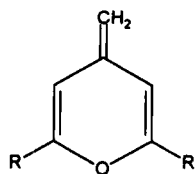
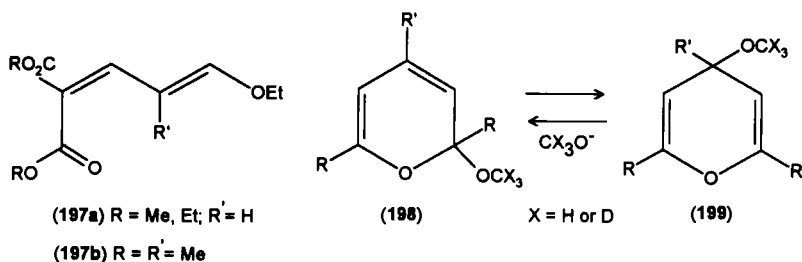
When subjected to pulse UV photolysis, several stable 2-dimethylamino-2*H*-pyrans afforded the corresponding short-lived open-chain tauto-

mers. Rate constants for the reverse reactions together with appropriate activation parameters have been reported (88KGS1325; 89IZV1323).

c. *Tautomerism of 2-Alkoxy-2H-pyrans and Alkoxydienones.* Surprisingly, negligible solvent effects and even no effects of the 3-methyl group have also been observed. Thus, 22% and 20% of 2-ethoxy-2*H*-pyrans **37** were found in their mixtures with tautomers **197a** equilibrated in CDCl_3 or CD_3OD . The dienone **197b** gave no 2*H*-pyran under various conditions (90IZV2561).

2. Mutual Isomerizations of Alkoxypryrans

Different kinetic and thermodynamic stabilities of isomeric 2-alkoxy-2*H*-pyrans **198** and 4-alkoxy-4*H*-isomers **199** stimulated systematic studies of their interconversions. As mentioned in Section V.C.4, such transformations have been considered to proceed via substituted pyrylium alkoxide intermediates and "ion pair-like" transition states [86JCS(P2)271; 88JOC1729]. Substituent effects were investigated in a series of 4-substituted 2,6-di-*tert*-butyl isomers **198a,b** (82JOC960; 86JCS(P2)271; 88JOC1729) and 4-substituted 2,6-diphenyl isomers **198c** [82JOC960; 86JCS(P2)271; 89JCS(P2)1393] using $\text{CD}_3\text{ONa}-\text{CD}_3\text{OH}$ reagents (for ^1H NMR monitoring) and $\text{CH}_3\text{ONa}-\text{CH}_3\text{OH}$ systems or $\text{Et}_3\text{N}-\text{Et}_3\text{NH}^+-\text{CH}_3\text{OH}$ buffers (for UV spectrophotometry).



(200) ($\text{R} = \text{tBu}$, Ph)

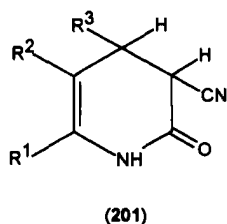
- (a) $\text{R} = \text{tBu}$; $\text{R}' = \text{H}$, Me , tBu , Et_3C , Ph
 (b) $\text{R} = \text{tBu}$; $\text{R}' = \text{XC}_6\text{H}_4$ ($\text{X} = 3\text{-Cl}$, 4-Cl , 4-Me , $4\text{-Me}_2\text{N}$, 4-MeO , 4-NO_2)
 (c) $\text{R} = \text{Ph}$; $\text{R}' = \text{H}$, Me , tBu , Ph , MeO

Experiments at -30°C to -40°C have shown mixtures of **198a–c** and **199a–c** to be products of kinetic control except for several extreme cases when 2*H*-pyrans **198a** ($\text{R} = \text{Me}, t\text{Bu}, \text{MeO}$) or 4*H*-pyrans **199a** ($\text{R} = \text{H}$), **199b** ($\text{X} = \text{Me}_2\text{N}$), and **199c** ($\text{R} = \text{H}$) were the only isomers formed initially [86JOC4385; 86JCS(P2)271; 88JOC1729; 89JCS(P2)1393]. These findings have been interpreted in terms of regioselectivity, reflecting charge densities in the intermediate pyrylium ions [86JCS(P2)271].

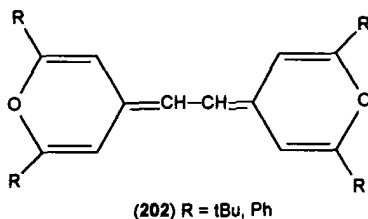
Experiments at $25^{\circ}\text{--}30^{\circ}\text{C}$ have shown 2*H*-pyrans **198a–c** to be almost exclusive products of thermodynamic control although sometimes only reaction artifacts were detected. Thus, 4-methylene derivatives **200** arose from 4*H*-pyrans **199a,c** ($\text{R}' = \text{Me}$) by spontaneous MeOH elimination at 25°C [86JCS(P2)271; 89JCS(P2)1393]; and, instead of unstable 2*H*-pyran **198c** ($\text{R}' = \text{H}$), only its valence-bond isomer was irreversibly formed [86JCS(P2)271]. The thermodynamic preference of the 4*H*-isomers **199c** was estimated to be about $4.6 \text{ kcal} \cdot \text{mol}^{-1}$ (86JOC4385), and it was concluded to be more heavily influenced by steric than by polar substituent effects [86JCS(P2)271]. A number of rate and equilibrium constants are available, especially in references 86JOC4385 and 88JOC1729.

3. Isomerizations of 2-Amino-3-cyano-4*H*-pyrans to 3-Cyano-3,4-dihydro-2*H*-pyridones

This ring-opening–ring-closing conversion of 4*H*-pyrans **166a** has been found to take place by heating with acidic reagents or AcONH_4 , affording variable yields of isomers **201** (86H1675; 86JPR35; 89LA145; 90CCC718; 91CCC2175) as shown in Table XVI. The isomerization of fused 4*H*-pyran



$\text{R}^1, \text{R}^2, \text{R}^3$, see Table XVI



44 ($\text{Ar} = \text{Ph}, \text{X} = \text{CN}$) with a $\text{AcONH}_4\text{--AcOH}$ reagent was reported to be accompanied by hydrolysis of the 3-CN substituent to a carboxamide group (89JPR971).

TABLE XVI
3-CYANO-3,4-DIHYDRO-2*H*-PYRIDONES **201** PREPARED BY
ISOMERIZATIONS OF 4*H*-PYRANS **116a**

R ¹	R ²	R ³	Reagent ^a	Yield (%)	References
H	CN	Ph	C	45	89LA145
Me	Ac	2-furyl	A	61	90CCC718
Me	CN	Ph	C	49	89LA145
Me	CO ₂ Et	Ph	C	71	89LA145
Me	CO ₂ Et	4-ClC ₆ H ₄	E	70 ^b	91CCC2175
Me	CO ₂ Et	4-MeOC ₆ H ₄	E	51 ^b	91CCC2175
Ph	CN	<i>i</i> Pr	C	50	89LA145
Ph	CN	Ph	D	46	86JPR35
Ph	CN	4-MeC ₆ H ₄	D	44 ^c	86JPR35
Ph	CN	4-MeOC ₆ H ₄	D	17 ^c	86JPR35
Ph	COPh	Ph	B	31 ^d	86H1675
Ph	COPh	4-MeOC ₆ H ₄	B	34	86H1675
Ph	CO ₂ Et	Ph	D	5 ^c	86JPR35
Ph	CO ₂ Et	4-MeOC ₆ H ₄	D	38	86JPR35

^a A: AcOH; B: AcOH-H₂SO₄; C: AcOH-H₂SO₄-H₂O; D: H₂SO₄-EtOH; E: AcONH₄.

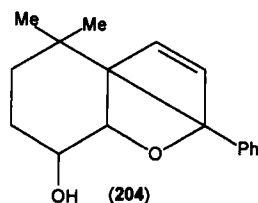
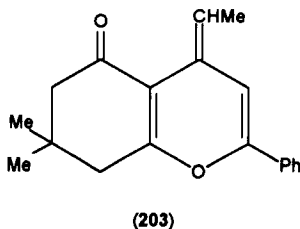
^b In addition to the corresponding 2-aminopyridine.

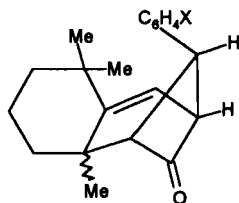
^c In addition to the corresponding 2*H*-pyridone.

^d In addition to a ring-opening product.

4. Miscellaneous

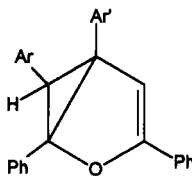
Acetylenic bis-4*H*-pyrans **101** were found to undergo a double exocyclic hydrogen shift to bispyranylidenes **202** on heating with *t*BuOK in DMSO (85LA708). The 3-membered ring in spirocyclic 4*H*-pyran **69b** (R = H, R' = Ph) was easily opened by aqueous acids, affording pyranylidene isomer **203** (89CB1285). 2*H*-Pyran **81b** (R¹ = R² = H, R³ = Me) was photochemically (λ > 280 nm) converted to a mixture of bridged stereoisomers **204** (85HCA192). Other bridged products **205** (75–80%) were prepared from arylethenyl 2*H*-pyran derivatives **81a** (R¹ = R² = H,





(205)

X = H, 4-Me, 4-MeO



(206)

(a) Ar = Ar' = Ph

(b) Ar = Ph, Ar' = 4-XC₆H₄ (X: Br, Me)(c) Ar = 4-XC₆H₄ (X: Br, Me), Ar' = Ph

R³ = XC₆H₄CH=CH) by UV illumination in MeO-H₂O, THF-H₂O, AcMe-H₂O, or aqueous dioxane (88CC1024). Analogously, 2,4,4,6-triaryl-4*H*-pyrans **8a,b** have been reported to be transformed into their photoisomers **206a** or **206b,c**, respectively, on the basis of ¹H and ¹³C NMR measurements [91JCS(P2)2061]. Some other isomerizations are mentioned in Sections V.C.1, V.F.1, and V.F.2.

D. RING-OPENING REACTIONS

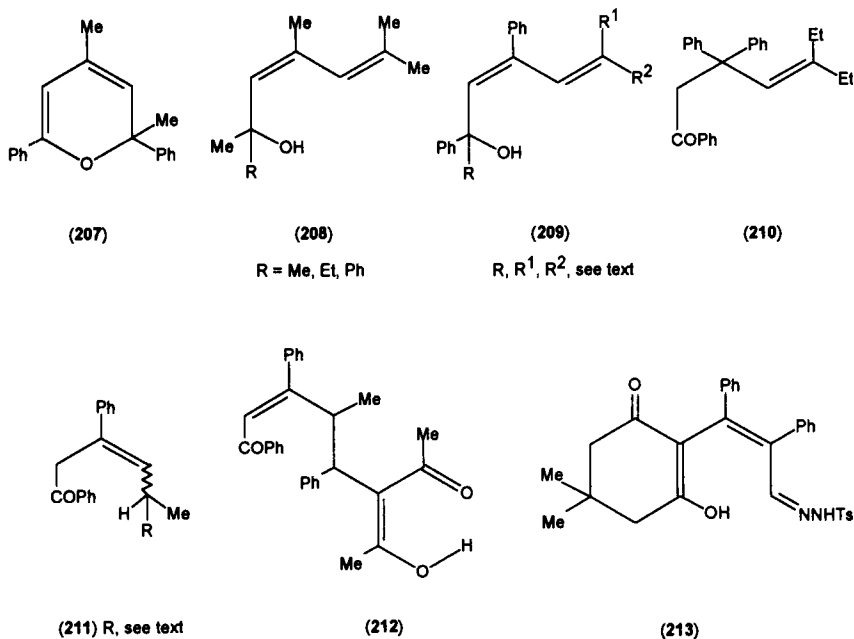
Various pyran-ring cleavages with different reagents have been reported in the last decade.

1. Cleavages of 2*H*-Pyrans

Typical ring openings associated with the valence-bond tautomerism of 2*H*-pyrans is discussed in Section V.D.1. Rereagents capable of causing the conversions include organometallics [87JCS(P1)2125], anions of C-acids (86JPR359), aqueous acids (84BCJ734; 84JPR657), oxidants, and hydrazines (84BCJ734).

Systematic investigations were performed on the reaction of organometallic reagents RLi, RMgI(Br), R₃Al, and R₂CuLi (R = Me, Et, *n*Bu, Ph) with 2,4,6-trisubstituted 2*H*-pyran **133** and 2,2,4,6-tetrasubstituted 2*H*-pyrans **107** (R = R' = Me), **145**, and **207** [87JCS(P1)2125]. Although all identified dienols and enones might be formally explained by nucleophilic attack of the starting molecules at positions 2, 4, or 6, the belief is that the reaction paths proceed via open-chain valence-bond tautomers of the 2*H*-pyrans. The transfer of an R group from a given organometallic reagent to the positions mentioned has been interpreted, then, as 1,2-, 1,4-, or 1,6-additions to appropriate dienones.

Thus, 2,2,4,6-tetramethyl-2*H*-pyran (**107**, $R = R' = \text{Me}$) gave the corresponding tertiary dienols **208** while 2,2-diethyl-4,6-diphenyl-2*H*-pyran **145**, in addition to analogous alcohols **209** ($R^1 = R^2 = \text{Et}$; $R = \text{Me, Et, Bu, Ph}$), afforded isomeric ketone **210** when PhMgBr was the reagent. 2-Methyl-4,6-diphenyl-2*H*-pyran **133** was converted to alcohols **209** ($R = \text{Me, Et, } n\text{Bu}$; $R^1, R^2 = \text{H, Me}$) but also to less expected ketone **211** ($R = \text{Bu}$), depending on organometallic reagents used. 2*H*-Pyran **207** has been shown to exhibit even lower regioselectivity, affording various products such as **209** and **211**; however, some of these products have not been proved with certainty [87JCS(P1)2125].



2-Dimethylamino- and 2-methoxy-2*H*-pyrans **121** ($\text{Ar} = \text{Ar}' = \text{Ph}$, $R = \text{H}$, $R' = \text{Me}$) and **128** ($R = \text{Me}$) reacted with a $\text{Ac}_2\text{CH}_2\text{-Et}_3\text{N}$ reagent to give open-chain product **212**, thus correcting older literature data (86JPR359). Diketone **126** ($\text{Ar} = \text{Ar}' = \text{Ph}$) was formed by hydrolysis of the above-mentioned 2*H*-pyran **121** in aqueous acetone (84JPR657). Fused 2-hydroxy-2*H*-pyran **176** was converted to tosylhydrazone **213** with TsNHNH_2 in EtOH (84BCJ734). (The oxidative decomposition of **176** to triketone **177** and diketone **178** is mentioned in Section V.A.6.) Other fused 2-alkoxy-2*H*-pyrans **214** obtained from the corresponding 2-alkylthiodienone with HgCl_2 in EtOH or $i\text{PrOH}$, respectively, were

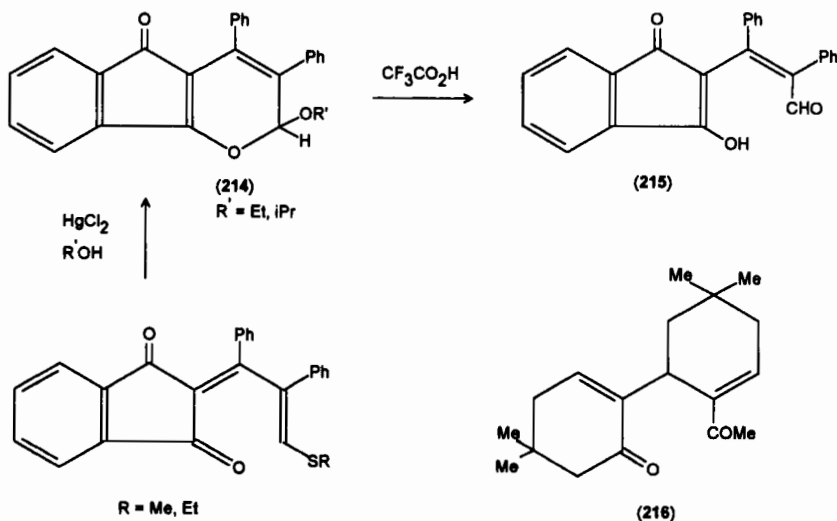
cleaved to enol-oxo aldehyde **215** with $\text{CF}_3\text{CO}_2\text{H}$ in CDCl_3 (Scheme 7) as observed by ^1H and ^{13}C NMR spectroscopy (84BCJ734).

2. Cleavages of 4H-Pyrans

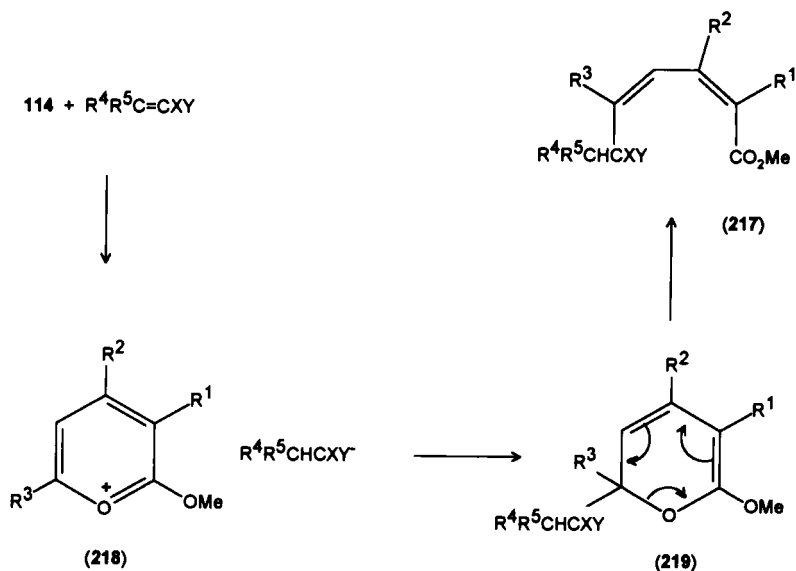
Ring openings of the 4H-pyran ring have been accomplished at times by heating (81CL1535) as well as with various agents such as complex hydrides (83ZOR2027), C-electrophiles (83JOC2736), aqueous acids (86H1675; 89CB1285; 90KF36), amines [86IJC(B)347; 90JCR(S)156], and other reactive systems (87TL6305; 89JOC1931; 89JOC1931).

4H-Pyrans **115** ($\text{R} = \text{H}$; $\text{R}' = \text{Me}$, Ph) were observed to undergo ring openings to stereoisomeric mixtures of betaines $\text{PhCOCH}=\text{CH}-\text{CH}=\text{CH}-\text{C}(\text{S}^+\text{Me}_2)=\text{C}(\text{O}^-)\text{Ph}$ on heating in acetonitrile (81CL1535).

4H-Pyran 3,5-diketone **22a** ($\text{R} = \text{H}$) was reduced to another diketone **216** with LiAlH_4 in Et_2O (83ZOR2027). A general ring-opening transformation of 2-methoxy-4H-pyrans **144** ($\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{H}, \text{Me}$; $\text{Me}, \text{H}, \text{H}$; $\text{Me}, \text{H}, \text{Me}$; $\text{Me}, \text{Me}, \text{H}$) to substituted methyl heptadienoates **217** was discovered in reactions of the starting heterocycles with sufficiently electrophilic ethenes $\text{R}^4\text{R}^5\text{C}=\text{CXY}$ ($\text{R}^4 = \text{H}, \text{Me}, \text{Ph}, \text{CN}, \text{CO}_2\text{Et}$; $\text{R}^5 = \text{Ph}, 4\text{-O}_2\text{NC}_6\text{H}_4, \text{H}, \text{CN}$; or $\text{R}^4, \text{R}^5 = (\text{CH}_2)_5$; $\text{X}, \text{Y} = \text{CN}, \text{CO}_2\text{Et}$). A probable mechanism (Scheme 8) involves initial hydrogen transfer from the 4H-pyrans **144** to the reagents affording ion-pairs **218** followed by recombination and ring-opening steps via 2H-pyran intermediates **219** (83JOC2736).

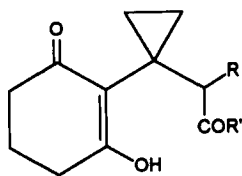
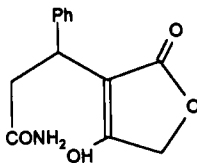


SCHEME 7

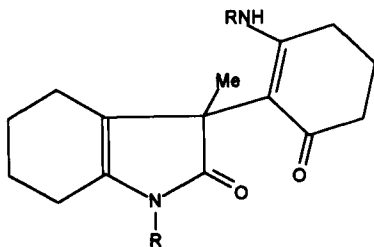
SCHEME 8 (R^1 to R^5 , X and Y; see text)

2,4,6-Triphenyl-4*H*-pyran **92** ($R = R' = Ph$) was reported to give diketone $PhCH(CH_2COPh)_2$ as a by-product after the subsequent actions of $POCl_3$ -DMF and NaOH reagents (89ZOR1342). Similar diketones **89** ($R = Me, Ph$) were shown to be products not of disproportionation but of hydrolysis from 2,3,4,5,6-trisubstituted 4*H*-pyrans **103** ($Ar = Ph$; $R^1 = R^2 = Me$; $R^3 = Me$ or Ph) with aqueous perchloric acid (90KF36). Analogously, acetic acid hydrolysis of spirocyclic 4*H*-pyrans **69b** gave open-chain products **220** and the same behavior was exhibited by other 2-ethoxy-4*H*-pyrans **71** and **72** (89CB1285). Hydrolytic cleavage of the 2-amino-3-cyano-4*H*-pyran ring system in **165** ($R^1 = R^3 = Ph$, $R^2 = PhCO$) with a H_2SO_4 -AcOH mixture yielded only 18% of the open-chain derivative $H_2NCOCH(CN)CH(Ph)CH(COPh)_2$ in addition to a prevailing 3,4-dihydro-2*H*-pyridone product (86H1675). The hydrolysis of fused 4*H*-pyran **46a** ($Ar = Ph$) proceeded analogously but with lactone-ring conservation, affording 40% of amide **221** (91LA827). 3,6-Dimethyl-2-cyano-4*H*-pyran underwent its decomposition to keto-carboxylic acid $MeCO(CH_2)_2CH(Me)CO_2H$ almost quantitatively in 20% hydrochloric acid (83TL2847). The cyano ester **165** ($R^1 = R^3 = Ph$, $R^2 = CO_2Et$) was earlier reported to give an open-chain product with 3-phenyl-5-aminopyrazole, but only $PhCH=NNHPh$ with phenylhydrazine (82M53).

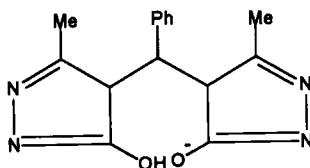
The cleavage of the heterocyclic ring in fused 4*H*-pyran-4-carboxylic

(220) R, R' = F, OEt; Me, Et₂N

(221)



(222) R = Bu, iPr



(223)

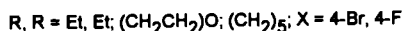
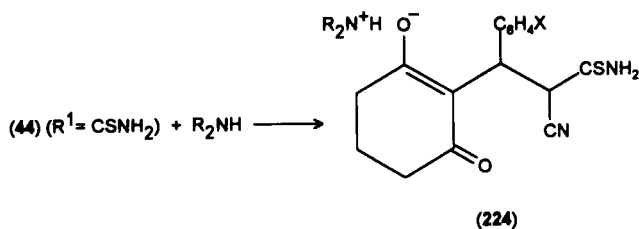
acid **54b** with hot ethanolic solutions of amines RNH₂ was found to be accompanied by ring retro-closures to final products **222** [86IJC(B)347]. Similar steps took place during the formation of the piperidinium salt of **223** from pyrazolo derivative **40** (R¹ = NH₂, R² = CN, Ar = R³ = Ph) on heating with ethanolic piperidine [90JCR(S)156]. On the other hand, no heterocyclizations have been observed in the cleavage reactions of fused 4-amino-4*H*-pyran-3-thioamides **44** (R¹ = CSNH₂; R² = 4-BrC₆H₄, 4-FC₆H₄; R³ = R⁴ = Me) with secondary amines R₂NH, affording enol-salts **224** (88ZOR460).

E. SUBSTITUTION REACTIONS

In the field of 4*H*-pyrans, knowledge of substitution reactions has been enriched thanks to recent investigations on metal-coordinated pyrans.

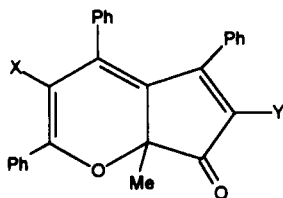
1. Substitution Reactions of 2*H*-Pyrans

Electrophilic bromination of the 2*H*-pyran ring in the fused derivative **110** (Ar = Ar' = Ph, R = Me) was found to proceed more slowly than that of the 5-membered carbocycle. Thus, dibromo derivative **225a** was obtained only with an excess of Br₂ in AcOH, while monobromo product



225b was formed using a 1 : 1 molar ratio of reactants. Attempts to nitrate the substrate with 65% HNO_3 in AcOH only resulted in the formation of nitro derivative **225c** (88ZC295; 89JPR293).

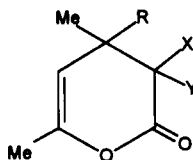
Nucleophilic replacements have been observed with 2*H*-pyrans possessing a good leaving group in position 2. Thus, 2-dimethylamino-3-methyl-2,4,6-triphenyl-4*H*-pyran was converted to 2-methoxy derivative



(225a) $X = Y = \text{Br}$

(225b) $X = \text{H, } Y = \text{Br}$

(225c) $X = \text{H, } Y = \text{NO}_2$



(226a) R , see text; $X = \text{Br, } Y = \text{H}$

(226b) $R = \text{Bu, 4-MeC}_6\text{H}_4$; $X, Y = \text{CH}_2$

128 ($R = \text{Me}$) on heating in methanol (84JPR657); similar 2-substitutions of **121**-like 4*H*-pyrans were reported earlier (81ZC282). The solvolyses of 2-alkylthio-2*H*-pyrans, such as **32**, **34**, and **35**, with MeOH , EtOH , or $i\text{PrOH}$ to corresponding 2-alkoxy-2*H*-pyrans (in yields of 61–93%) were found to occur readily in the presence of HgCl_2 by trapping the eliminated H_2S . The 2-substitution by a hydroxy group to afford hemiacetal **176** was achieved with a $\text{Hg}(\text{OAc})_2\text{--AcOH}$ reagent (83H1013; 84BCJ734).

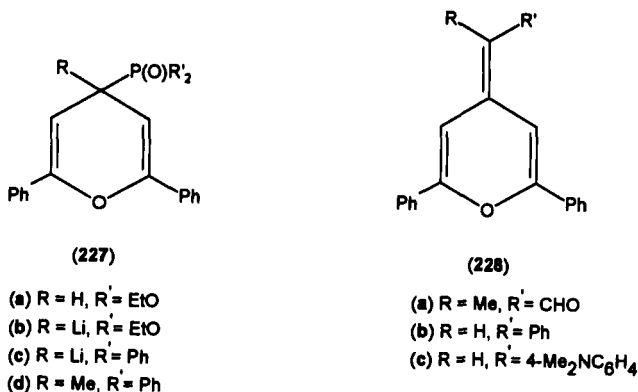
2. Substitution Reactions of 4*H*-Pyrans

As briefly mentioned in Section III.A, 2,4,4,6-tetraphenyl-4*H*-pyran (**8a**) was chlorinated, brominated, and even nitrated under mild conditions in positions 3 and 5 to appropriate derivatives **12a** ($X = Y = \text{Cl, Br, NO}_2$) (92CCC546). Vilsmeier–Haack formylations of **6a** (89AP617) and **8a**

(92CCC2383) yielded 3-carbaldehydes **6** ($R = iPr$, Ph ; $R' = CHO$; $Ar = Ph$, $3-O_2NC_6H_4$) and **12b** (92CCC2383), while the same procedure with 2,4,6-triphenyl-4*H*-pyran (**92c**) led only to a mixture of analogous 3-formyl derivative and diketone $PhCOCH=C(Ph)CH_2COPh$ (89ZOR1342, 90KGS603).

Bromination of a number of 2-trialkylsilyloxy-4*H*-pyrans **106b** (R , see Section IV.A.2.c) initially gave unstable 3-bromo derivatives, spontaneously eliminating $tBu(Me)_2SiH$ and yielding mixtures (56% and 92%) of *cis-trans* stereoisomeric 2,3-dihydro-2*H*-pyrones **226a**. The electrophilic reagent $CH_2=NEt_3^+Cl^-$ started analogous reaction paths, giving 3-methylene products **226b** apparently after the elimination of $tBu(Me)_2SiNEt_3$ (87TL6305; 89JOC1931). Similar reactions (91S375) are discussed in Section V.G.1.

Modified electrophilic substitutions of 4*H*-pyrans proceeding via the corresponding 4-lithio intermediates have been further extended. Thus, phosphonic ester **227a** was lithiated to the Wittig–Horner reagent **227b**, giving 35% of aldehyde **228a** after the addition of $MeCOCH(OMe)_2$ and subsequent acidic hydrolysis (82JOC680). Lithio derivative **227c**, similarly prepared from **131** ($R = Ph$), was converted to 4-substituted products **227d** and **228b,c** using MeI or appropriate aldehydes $R'CHO$, respectively (90ZOB1012).

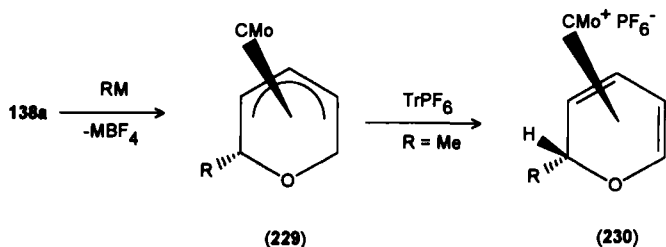


A rare nucleophilic 4-substitution of the 4*H*-pyran ring could be recognized as a typical addition–elimination process in the hydrolysis of spirocyclic derivative **69a** into the corresponding 4*H*-pyrone with dilute hydrochloric acid (90ACS833).

3. Substitution Reactions of Metal-Coordinated Pyrans

Optically active tetrafluoroborates and hexafluorophosphates containing 2*H*-pyran (**1**) or its 2- and 2,6-substituted derivatives as ligands

together with the molybdenum component $(\text{CO})_3\text{MoC}_5\text{H}_5$ (abbreviated CMo) in complex cations have been found to undergo easy substitutions with C-nucleophiles. Regio- and stereospecificities of reaction similar to those with complex hydrides (see Section V.B.2) were recognized in the stepwise conversions of ligand **1** in **138a** to 2-substituted neutral complexes **229** (Table XVII) and salt **230** with subsequent action of organometallic



CMo = $\text{Mo}(\text{CO})_3\text{C}_5\text{H}_5$; R and Me, see Table XVII

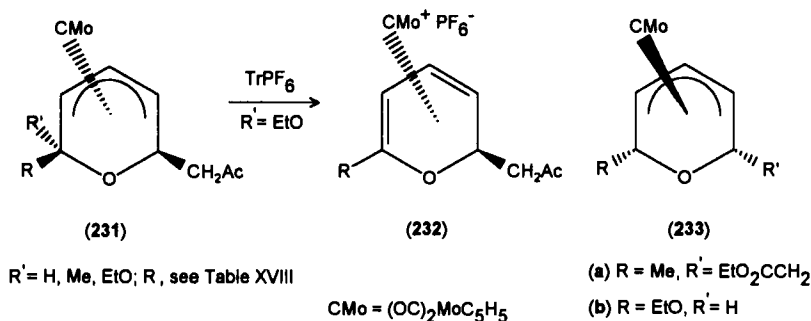
reagents RM and Tr^+PF_6^- , respectively (90JA9660). The first of these steps has been realized in many cases. As shown in Table XVIII, the reactions of other Mo-coordinated 2*H*-pyrans **190** ($\text{R} = \text{H}, \text{Me}, \text{EtO}$) with $\text{R}'\text{M}$ reagents gave nonionic complexes **231** in satisfactory yields. The second oxidative step **231** \rightarrow **232** was accomplished only with selected substrates ($\text{R} = \text{EtO}$) using Tr^+PF_6^- in CH_2Cl_2 (93JA891). Analogously, **230** was converted with $\text{LiCH}_2\text{CO}_2\text{Me}$ (-78°C , THF) to **233a** and nonionic complex **233b** to coordinated 2*H*-pyran **138a** with HBF_4 in Et_2O in the enantiomeric series (90JA9660, 93JA891).

Manganese coordinated 4*H*-pyrans **92** ($\text{R} = i\text{Bu}, \text{Ph}$; $\text{R}' = \text{C}_5\text{H}_5\text{Mn}(\text{CO})_3$), in which the heterocycle is covalently bound to the cyclopentadiene ring, were found to be capable of simple ligand replacements of one CO group for Ph_3P (85KGS593). Similar behavior was exhibited by some

TABLE XVII
REACTIONS OF MO-COORDINATED 2*H*-PYRANS **138a** WITH ORGANOMETALLICS
(90JA9660)

R	M	Yield of 229 (%)	R	M	Yield of 229 (%)
Me	Li	56	4-MeC ₆ H ₄	MgBr	82
Me	MgI	80	CH ₂ Ac	Li ^a	68
CH ₂ =CH	MgBr	64	CH ₂ CO ₂ Me	Li	76
BuC≡C	Li	66	CH(CO ₂ Et) ₂	Na	90

^a With $\text{LiCH}_2\text{C}(\text{Me})=\text{NC}_6\text{H}_{11}$ and subsequent hydrolysis.



Pt-coordinated complexes of 2,4,6-trifluoromethyl-2-methyl-2H-pyran [80JCS(D)2095].

F. CONVERSION TO CARBOCYCLIC SYSTEMS

Novel examples of intramolecular recyclizations of 2H-pyrans to benzoic products have been reported in the last decade. 4H-Pyrans have been converted to cyclohexene and cyclobutene systems.

1. Conversions of 2H-Pyrans

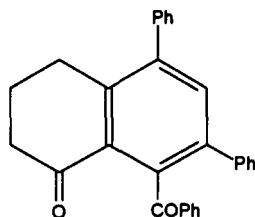
2H-Pyrans possessing substituents with an active methylene fragment in position 2 generally could be converted via their valence-bond tautomers to substituted benzenes with basic reagents [81ZC446; 83AHC(34)145]. Thus, tetralone-like diketone **234** was obtained from fused 2H-pyran **111**

TABLE XVIII
REACTIONS OF MO-COORDINATED HEXAFLUOROPHOSPHATES **190** WITH
ORGANOMETALLIC COMPOUNDS (93JA891)

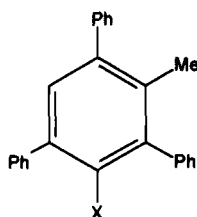
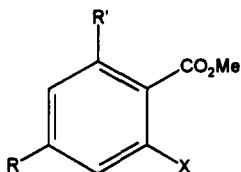
R'	RM	Yield of 231 (%)	R'	RM	Yield of 231 (%)
H	MeMgI	86	Me	BuMgBr	67
H	CH ₂ =CHMgBr	84	EtO	MeMgI	87
H	BuC≡CLi	83	EtO	EtMgBr	74
H	BuC≡CMgBr	51	EtO	BuC≡CLi	89
H	4-MeC ₆ H ₄ MgBr	81	EtO	BrMg≡CMgBr	59
H	MeO ₂ CCH ₂ Li	85	EtO	4-MeC ₆ H ₄ MgBr	84
H	(MeO ₂ C) ₂ CHNa	82	EtO	MeO ₂ CCH ₂ Li	84
Me	MeMgI	63	EtO	(MeO ₂ C) ₂ CHNa	— ^a

^a No **231**-like products were formed.

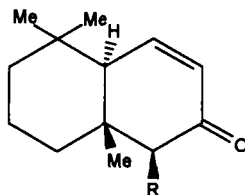
(Ar = Ar' = Ph) in 72% yield on heating with AcONa–EtOH (89JPR306). The precursors could be generated *in situ* from 2-methoxy- and 2-dimethylamino-2*H*-pyrans, as found in the preparations of benzene derivatives **235** from starting heterocycles **121** (Ar = Ar' = Ph, R = H, R' = Me) and **128** (R = Me) with NCCH₂CO₂Et–Et₃N and MeNO₂–Et₃N reagents, respectively (83JPR729; 84JPR657).



(234)

(235) X = CN, NO₂(236a) R = R' = Me, X = CO₂Me

(236b) R = Cl, R' = H, X = H

(236c) R = Cl, R' = Ph, X = CO₂Me

(237a) R = Me

(237b) R = CH₂CO₂Me

The following spontaneous decompositions of cycloadducts of 2,2,4,6-tetrasubstituted 2*H*-pyrans with acetylenic esters MeO₂CC≡CCO₂Me (DMAD) and HC≡CCO₂Me (MAC) to benzene derivatives were reported: **107** (R = R' = Me) + DMAD → **236a** + AcMe (83JA1263), **148** + MAC → **236b** + AcMe, and **148** + DMAD → **236c** + AcMe (91HCA27).

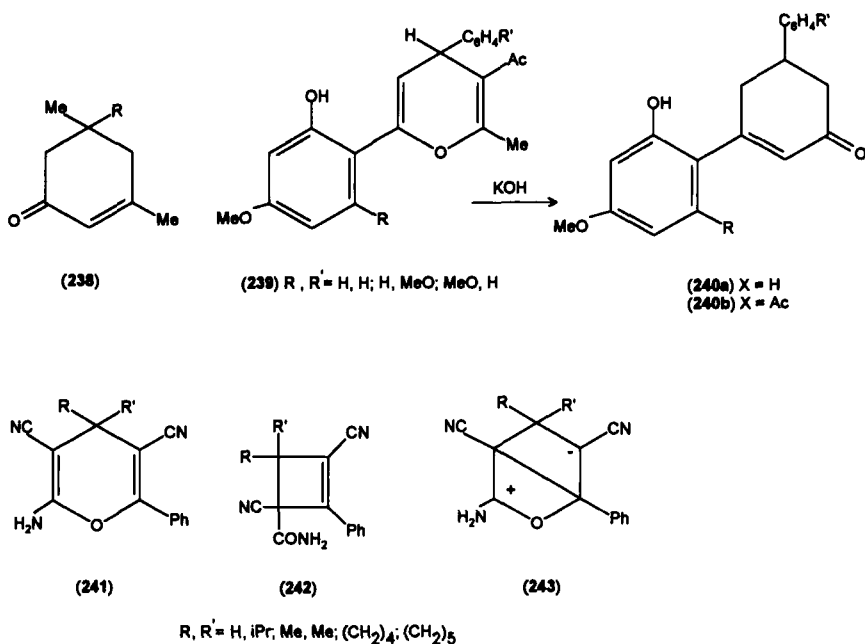
Ultraviolet photolysis of fused 2*H*-pyran **81a** (R' = R² = H, R³ = CHCO₂Me) using a pyrex filter and MeONa–MeOH gave a 1 : mixture of ketone **237a** and keto-ester **237b** (85JOC1939).

2. Conversions of 4*H*-Pyrans

Hydrolytic cleavage of 2,4,4,6-trisubstituted 4*H*-pyrans **106** (R = nC₈H₁₇, PhCH₂CH₃, 4-MeC₆H₄) with HCl–H₂O–MeCN resulted in

high yields of the corresponding cyclohexenones **238** (87H1495). 4*H*-Pyrans **239** were converted to cyclohexenones **240a**, apparently via unisolable diketones **240b**, by heating with KOH–EtOH–H₂O (83H2369).

2-Amino-3,5-dicyano-4*H*-pyrans **241** were isomerized to cyclobutene carboxamides **242** on UV-illumination using a pyrex filter. This interesting conversion has been shown to proceed via excited triplet states of **241** and is thought to involve intermediate **243**. The subsequent photoproducts were $\text{PhC}\equiv\text{CCN}$ and cyanocarboxamides $\text{R}_2\text{C}\equiv(\text{CN})\text{CONH}_2$ (87CC1231; 89JOC3069).



G. CONVERSION TO OTHER HETEROCYCLES

Numerous preparative investigations have been devoted to the conversions of 4*H*-pyrans to various heterocyclic systems. We discuss here only those transformations in which the pyran ring is not conserved. Other cases will be considered as functional-group transformations and discussed in Section V.J. Some conversions of pyrans to heterocyclic compounds have also been mentioned in Sections V.A.3, V.C.3, and V.C.4.

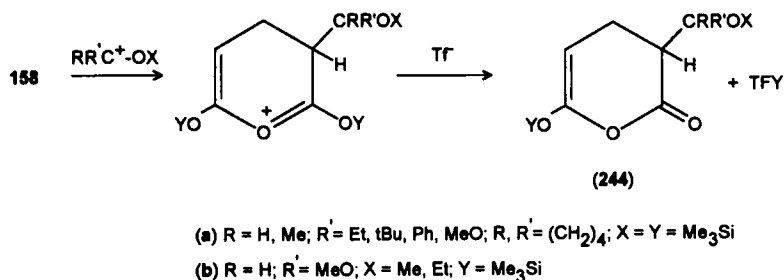
1. Conversion of 4*H*-Pyrans to Dihydro-2*H*-pyrones and Tetrahydropyran-2,6-diones

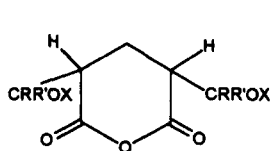
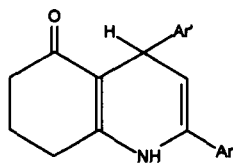
As mentioned in Section V.E.2, 2-trialkylsilyloxy-4-pyrans **106b** undergo electrophilic substitution in position 3 and subsequent trialkylsilan elimination, affording 2,3-dihydro-2*H*-pyrones **226** (89JOC1931). An extension of this approach to 2,6-bis(trimethylsilyloxy)-4*H*-pyran (**158**) made it possible to obtain 3,5-disubstituted tetrahydropyran-2,6-diones **245** (91S375) in addition to 226-like derivatives **244**. The starting 4*H*-pyran **158** was treated with carbonyl compounds $RR'C=O$ or acetals $RR'(OX)_2$ activated with trimethylsilyl triflate ($RR'CO + TfY \rightarrow RR'C^+OY + Tf^-$ and $RR'(OX)_2 + TfY \rightarrow RR'C^+OX + Tf^- + XOY$, where $Tf = OSO_2CF_3$ and $Y = Me_3Si$), yielding 66 to 95% of dihydropyrones **244a,b** according to Scheme 9. The use of a double excess of the reagents caused subsequent conversion of intermediates **244** to tetrahydropyran-2,6-diones **245a** ($R' = Ph, 4-ClC_6H_4, 4-MeOC_6H_4, 4-Me_2NC_6H_4, 4-O_2NC_6H_4$) and **245b**, also in high yields (65–95%).

2. Conversion of 4*H*-Pyrans to 1,4-Dihydropyridines

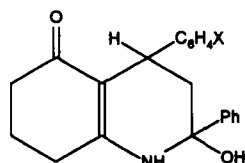
Various 1,4-dihydropyridines have been reported to arise from 4*H*-pyrans by the action of ammonia (83ZOR2027; 90KGS511), aniline (84JPR248), hydrazine hydrate (87JHC1677), ammonium acetate (89JPR971; 89LA145; 91LA827), and even by heating with morpholine (88ZOR460; 90ZOR1578). In some cases, instead of the expected 1,4-dihydro derivatives, the corresponding pyridines were obtained by using ammonium acetate (89LA145).

1,4-Dihydropyridines **246** were prepared from the corresponding 4*H*-pyrans **16** ($R^1 = H, R^2 = Ar', R^3 = Ar$) by heating in NH_3-EtOH . A complete mechanism of cyclocondensation has been proposed in

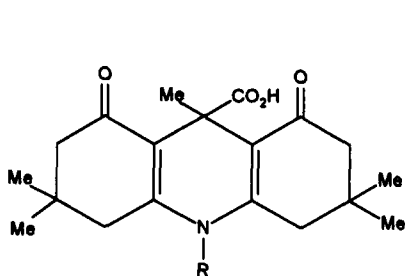
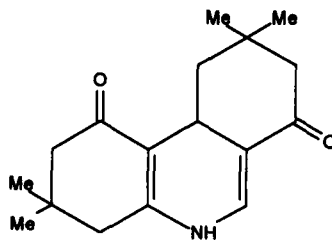


(245a) $R = H$; $R' =$, see text; $X = \text{Me}_3\text{Si}$ (245b) $R = H, \text{Me}$; $R' = H, \text{Me}, \text{MeO}$; $X = \text{Me}, \text{Et}$ 

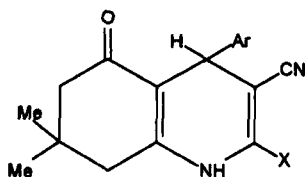
(248)

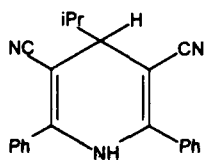
 $\text{Ar} = \text{Ph}, 4\text{-MeC}_6\text{H}_4$ $\text{Ar}' = \text{Ph}, 4\text{-MeOC}_6\text{H}_4, \text{O}_2\text{NC}_6\text{H}_4$ (247) $X = 4\text{-MeO}$

agreement with the trapping of intermediate **247** (90KGS511). Other fused 1,4-dihydropyridines were also obtained from analogous 4*H*-pyrans with certainty—namely, **248** from **54b** using $\text{AcONH}_4\text{--AcOH}$ and $\text{PhNH}_2\text{--MeOCH}_2\text{CH}_2\text{OH}$, respectively [86IJC(B)347]; **249** from **22a** ($R = \text{Me}$) with NH_3 (83ZOR2027); and **250a** from **44** ($R^1 = \text{CN}$, $R^2 = \text{Ar}$, $R^3 = R^4 = \text{Me}$) with $\text{AcONH}_4\text{--AcOH}$ (89JPR971). On the other hand, tautomeric 1,4-dihydropyridines **250b** and their salts were found to possess 2- and 3-substituents (SH, CN) different from those of the starting 4*H*-pyrans **44** ($R^1 = \text{CSNH}_2$, $R^2 = \text{Ar}$, $R^3 = R^4 = \text{Me}$) owing to thioamide group participation in the reaction with hot ethanolic morpholine (88ZOR460; 90ZOR1578). Evidently, similar mechanisms were also responsible for the formation of symmetrically substituted 1,4-dihydropyridines **251** and **252** from differently substituted precursors **165** ($R^1 = \text{Ph}$, $R^2 = \text{CN}$, $R^3 = i\text{Pr}$) and **46a** ($\text{Ar} = \text{Ph}$, $R = \text{H}$) with $\text{AcONH}_4\text{--AcOH}$ (89LA145; 91LA827).

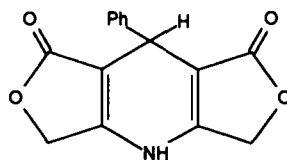
(248) $R = H, \text{Ph}$ 

(249)

(250a) $\text{Ar} = \text{Ph}, 2\text{-ClC}_6\text{H}_4$; $X = \text{NH}_2$ (250b) $\text{Ar} = 4\text{-BrC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4$; $X = \text{SH}$



(251)



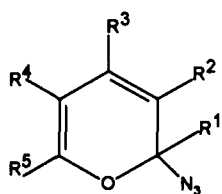
(252)

Some reports on the preparation of 2-hydroxy-1,4-dihydropyridines (84JPR248; 87JHC1677) are probably incorrect because of possible tautomerization of the compounds.

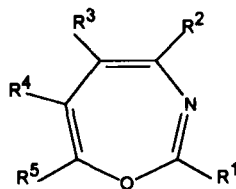
3. Ring Contraction and Expansion in Pyrans

The oxidative ring contraction of 6-substituted 4-chloro-3-methyl-2*H*-pyrans to furan derivatives **175** (87KGS418; 90ZOR965) is discussed in Section V.A.5.

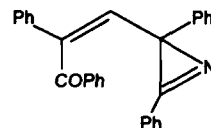
Novel examples of the known decomposition of labile 2-azido-2*H*-pyrans **253** to the corresponding 1,3-oxazepines **254** ($R^1 = R^2 = R^3 = R^4 = R^5 = \text{Ph}$; $R^1 = R^2 = R^3 = R^5 = \text{Ph}$, $R^4 = \text{H}$; $R^1 = R^3 = R^5 = \text{Ph}$, $R^4 = \text{H}$, $R^2 = 4\text{-BrC}_6\text{H}_4$; $R^1 = \text{Ph}$, $4\text{-MeC}_6\text{H}_4$, $R^2 = i\text{Pr}$, $R^3 = R^5 = \text{Ph}$, $R^4 = \text{H}$) have been reported. 2*H*-Pyrans **253** ($R^1 = R^2 = R^4 = R^5 = \text{Ph}$, $R^3 = \text{H}$) exhibited, however, exceptional behavior



(253)



(254)



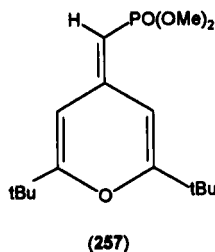
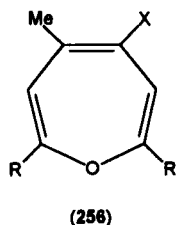
(255)

R^1 to R^5 , see text

by giving relatively stable azirine **255**, which isomerized to **254** only at 100°C (84T3559).

A new approach to oxepines **256a,b** from 4*H*-pyran 4-diazo compounds **116b,c** and **117** ($R^2 = \text{Me}$) involving initial N_2 elimination and subsequent ring expansion was found to be accomplished in high yields with allylpalladium chloride in benzene at 20°C (83TL5355; 85S569; 87JOC3851). In the cases of **116a** and **117** ($R^1 = R^2 = R^5 = \text{Me}$, $R^3 = R^4 = \text{MeO}$) the corresponding 1*H*-1,2-diazepines were also isolated (87JOC3851). The use

of copper(I) chloride catalyst led to a lower chemoselectivity, affording a mixture of oxepine **256a** ($X = \text{PO}(\text{OMe})_2$) and its 4-pyranylidene isomer **257** (85CB3700).

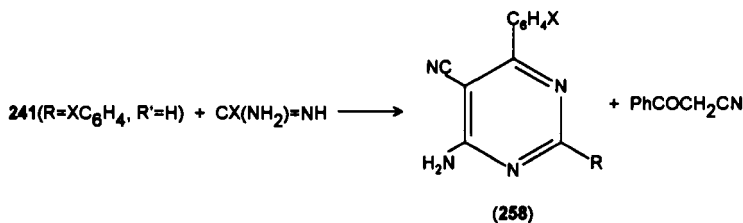


- (a) $R = t\text{Bu}$; $X = \text{COOEt}, \text{PO}(\text{OMe})_2, \text{PO}(\text{OMe})\text{Ph}, \text{POPh}_2$
 (b) $R = \text{Me}, \text{Ph}$; $X = \text{COOEt}, \text{PO}(\text{OMe})_2$

4. Conversions of 2-Amino-3-cyano-4H-pyrans

6-Amino-5-cyanopyrimidines **258a,b** were found to be generally formed by a ring-cleavage conversion of 2-amino-3,5-dicyano-4H-pyrans **241** with amidine reagents (86JPR35; 88SL203). The transformation of similar 3-cyano-5-ethoxycarbonyl-4H-pyrans with guanidine proceeded analogously, leading to **258a** and $\text{PhCOCH}_2\text{CO}_2\text{Et}$ (86JPR35). On the other hand, treatment of **241** ($R = \text{Me}$, $R' = \text{Ph}$) with $\text{AcONH}_4\text{-AcOH}$ resulted in a mixture of 6-amino-3-cyano-2,4-diphenylpyridine, $\text{PhC}(\text{Me})=\text{CN}_2$, and PhCOCH_2CN [90JCR(S)310].

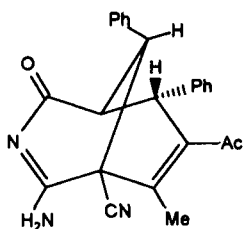
Various 2-amino-3-cyano-4H-pyrans have been observed to react with arylidene malonitriles and related derivatives to afford new fused heterocyclic compounds. The structure for a product from 4H-pyran



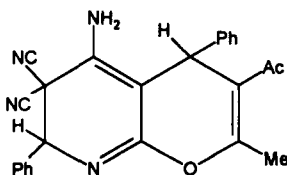
- (a) $R = \text{NH}$; $X = \text{H}, 4\text{-Me}, 4\text{-MeO}$
 (b) $R = \text{Me}, \text{SH}, \text{SMe}$; $X = \text{H}$

165 ($R^1 = \text{Me}$, $R^2 = \text{Ac}$, $R^3 = \text{Ph}$) and $\text{PhCH}=\text{C}(\text{CN})_2$ was determined by X-ray diffraction to be **259** (92T1581) instead of the earlier presumed **260** (88T5861). A multistep mechanism was postulated (92T1581). Hence, other postulated **260**-like structures (88T5861; 89JPR971; 91CCC2175; 91JPR345) probably should be revised. Other heterocyclic systems have been reported for similar cyclocondensations—namely, **241** ($R = R' = \text{H}$) + $\text{CH}_2 = \text{C}(\text{CN})_2 \rightarrow$ **261a** [91JCR(S)116], **165** ($R^1 = \text{Me}$, $R^2 = \text{CO}_2\text{Et}$, $R^3 = 4\text{-XC}_6\text{H}_4$) + $\text{CH}_2(\text{CN})_2 \rightarrow$ **261b**, and **165** ($R^1 = \text{Me}$, $R^2 = \text{CO}_2\text{Et}$, $R^3 = \text{XC}_6\text{H}_4$) + $\text{NCCH}_2\text{CONH}_2 \rightarrow$ **262** (89LA585). Pyrazolopyridone **263** was isolated after the reaction of 4*H*-pyran **45** ($R^1 = \text{CN}$, $R^2 = R^4 = \text{H}$, $R^3 = \text{Me}$) with sodium ethoxide [91JCR(S)116].

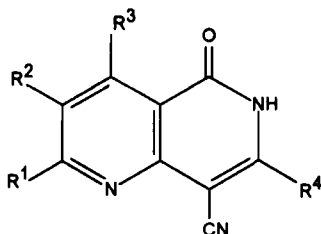
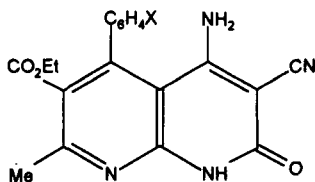
Some fused 2-amino-3-cyano-4*H*-pyrans **47b** were converted to appro-



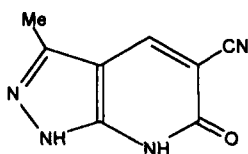
(259)



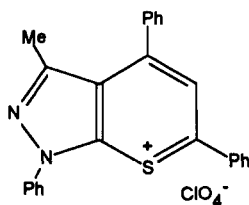
(260)

(261a) $R^1 = \text{Ph}$, $R^2 = \text{CN}$, $R^3 = R^4 = \text{H}$ (261b) $R^1 = \text{Me}$; $R^2 = \text{CO}_2\text{Et}$; $R^3 = 4\text{-ClC}_6\text{H}_4$, $4\text{-MeOC}_6\text{H}_4$, $2\text{-ClC}_6\text{H}_4$ 

(262)

 $X = 2\text{-Cl}$, 4-Cl , 4-MeO 

(263)



(264)

appropriate 2-alkoxypyridines with EtONa, PrONa, or *t*BuONa in their corresponding alcohols [88JCR(S)10].

5. Miscellaneous

Some 2,4,4,6-tetraaryl-4*H*-pyrans **8** ($\text{Ar}^1 = t\text{BuC}_6\text{H}_4$, $\text{Ar}^2 = \text{Ar}^3 = \text{Ph}$; $\text{Ar}^1 = \text{Ph}$, $\text{Ar}^2 = \text{Ar}^3 = 4-t\text{BuC}_6\text{H}_4$, 4- BrC_6H_4 , 4- FC_6H_4) were converted to analogous 4*H*-thiopyrans by heating with P_4S_{10} in xylene [92JCS(P2)1301] while pyrazolo-4*H*-pyran **40** ($\text{Ar} = \text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{H}$) gave the corresponding thiopyrylium perchlorate **264** with the same reagent and subsequent treatment with HClO_4 (82KGS317).

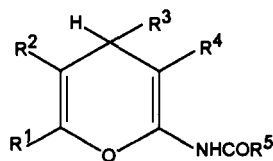
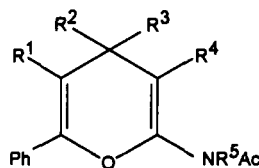
H. FUNCTIONAL-GROUP TRANSFORMATIONS

A number of functional-group transformations have been accomplished in substituted 4*H*-pyrans. Simple conversions and those leading to heterocyclic-ring closures will be discussed separately.

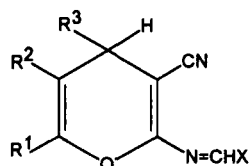
1. Simple Conversions in 4*H*-Pyrans

a. *Substitutions in the 2-Amino Groups.* A number of newly prepared 2-amino-4*H*-pyrans were smoothly *N*-acylated to the corresponding 2-acylamino derivatives **265** with Ac_2O [82M53; 86H1675; 86JPR35; 91IJC(B)25], ClCH_2COCl [90IJC(B)1020], and SCNCO_2Et [82RPQ133; 86ZN(B)925]; see Table XIX. Sometimes a second alkyl or acyl group was introduced at the nitrogen—namely, **165** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Ph}$) + 2 $\text{Ac}_2\text{O} \rightarrow \text{266a} + 2\text{AcOH}$ (86H1675), **241** ($\text{R} = \text{R}' = \text{H}$) + $\text{AcCl}(\text{C}_5\text{H}_5\text{N}) \rightarrow \text{266b} + \text{HCl}(\text{C}_5\text{H}_5\text{N})$ (89JOC3069), and **266c** + $\text{BrCH}_2\text{CO}_2\text{Et} \rightarrow \text{266d} + \text{HBr}$ [91IJC(B)25]. Reactions with *ortho*-ester $(\text{EtO})_3\text{CH}$ usually gave the corresponding *N*-ethoxyethylene derivatives **267** ($\text{X} = \text{EtO}$), namely **267a** (84CCC2309) and **267b**, which are capable of further transformation to amidines ($\text{X} = \text{NH}_2$) with $\text{NH}_3\text{--EtOH--H}_2\text{O}$ (88SOC399; 89CCC1336). Analogous *N*-substitution with PhPCl_2 (88CZ309) will be discussed in Section I.2 (Scheme 15).

b. *Transformations of the Carbonyl Group.* Substituted 3-formyl-4*H*-pyrans **268** were found to exhibit typical reactions of the aldehyde group, such as the formation of oximes ($\text{R} = i\text{Pr}$), semicarbazides ($\text{Ar} = \text{Ph}$, $\text{R} = i\text{Pr}$), and 2,4-dinitrophenyl hydrazones ($\text{Ar} = 3\text{-O}_2\text{NC}_6\text{H}_4$). Borohydride reduction of **268** afforded primary alcohols **269a**, which could be transformed to the corresponding acetyl and 4-nitrobenzoyl derivatives

(265) R^1 to R^5 , see Table XIX

(266)



(267) X, see text

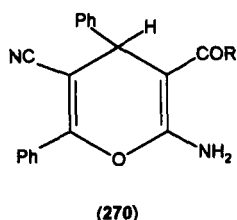
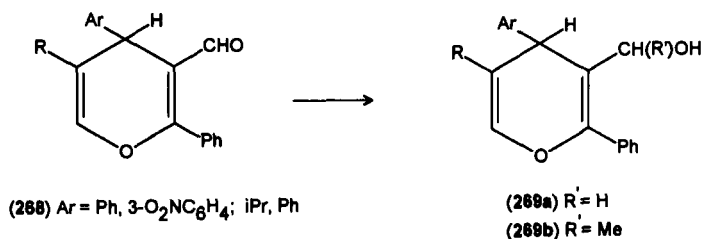
(a) $R^1 = R^2 = \text{Ph}$, $R^3 = \text{H}$, $R^4 = \text{CN}$, $R^5 = \text{Ac}$ (b) $R^1 = R^4 = \text{CN}$, $R^2 = R^3 = \text{Me}$, $R^5 = \text{Ac}$ (c) $R^1 = \text{CN}$, $R^2 = \text{Ph}$, $R^3 = R^5 = \text{H}$, $R^4 = \text{COOEt}$ (d) $R^1 = \text{CN}$, $R^2 = \text{Ph}$, $R^3 = \text{H}$, $R^4 = \text{CO}_2\text{Et}$, $R^5 = \text{CH}_2\text{CO}_2\text{Et}$ (a) $R^1 = 4\text{-PhC}_6\text{H}_4$, $R^2 = \text{CN}$, $R^3 = \text{Ph}$ (b) $R^1 = \text{Me}$; $R^2 = \text{Ac}$, COOEt ; $R^3 = 5\text{X-2-furyl}$ ($\text{X} = \text{H}$, CO_2Me , PhS)

on treatment with $\text{AcCl-C}_5\text{H}_5\text{N}$ or $4\text{-O}_2\text{NC}_6\text{H}_4\text{COCl-C}_5\text{H}_5\text{N}$, respectively. The Grignard reaction with MeMgI yielded the expected secondary alcohol **269b** ($\text{Ar} = \text{Ph}$, $\text{R} = i\text{Pr}$) (89AP617). The Wittig reaction with 6-formyl-2H-pyran **134c** to give α,β -unsaturated ester **134b** (93SY557) was mentioned in Section IV.D.1.

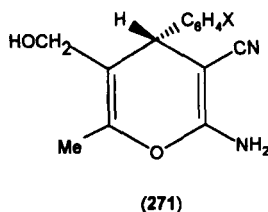
TABLE XIX
2-ACYLAMINO-4H-PYRANS PREPARED BY N-ACYLATIONS

Reagent	R^1	R^2	R^3	R^4	R^5	References
Ac_2O	Ph	Ph	Ph	CN	Me	86H1675
Ac_2O	Ph	CN	Ph	CN	Me	86JPR35
Ac_2O	Ph	CN	Ph	CO_2Et	Me	82M53 ^a
Ac_2O	Ph	CN	4-MeC ₆ H ₄	CN	Me	86JPR35
Ac_2O	Ph	CN	4-ClC ₆ H ₄	CN	Me	86JPR35
Ac_2O	Ph	CO_2Et	Ph	CN	Me	86JPR35
Ac_2O	Ph	CO_2Et	4-MeC ₆ H ₄	CN	Me	86JPR35
ClCH_2COCl	Ph	CN	Ph	CONHPy^b	ClCH_2	90IJC(B)1020
SCNCO_2Et	Me	CN	Ph	CN	EtO	86ZN(B)925
SCNCO_2Et	Ph	CN	Ph	CN	EtO	83RPQ133

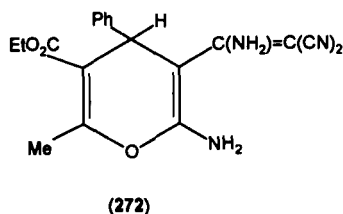
^a See also 91IJC(B)25.^b $\text{Py} = 2\text{-pyridyl}$.



- (a) R = EtO
(b) R = Ph
(c) R = OH
(d) R = 2-pyridylNH



X = H, 4-Br, 4-Cl, 2-Me, 4-Me, 3-NO₂



c. *Transformations of the Carboxylic Acid Group.* Methyl-4*H*-pyran-2,6-dicarboxylate was prepared from its dicarboxylic acid by heating with HC(OMe)₃-MeOH-H₂SO₄ (87CJC704). Fused 4*H*-pyran 4-carboxylic acid **54b** was converted to its methyl ester with CH₂N₂ in Et₂O [86IJC(B)347].

d. *Transformations of the Ester Group.* Borohydride reduction of 3-ethoxycarbonyl-4*H*-pyran **6b** afforded primary alcohol **269a** (89AP617). On the other hand, the reaction of ethyl ester **270a** with PhMgBr stopped at the ketone **270d** (82M53). Hydrolysis of ester **270a** by heating with NaOH-EtOH-H₂O resulted in 3-carboxylic acid **270c**, while 3-carboxamide **270d** was obtained by treatment with 2-aminopyridine [90IJC(B)1020]. The methoxycarbonyl group in Mo-coordinated derivative **233a** was hydrolyzed by heating with KOH-MeOH-H₂O with retention of the configuration (90JA9660).

e. *Transformations of the Carboxamide Group.* Optically active 4*H*-pyran-3-yl methanols of absolute configuration **271** were isolated in 40–73% yields after reduction of Oppolzer's sultamides **52** with $\text{LiAlH}_4\text{--Et}_2\text{O}$ (93TL5627).

f. *Miscellaneous Transformations.* A somewhat surprising behavior of the 3-cyano group in cyano ester **149b** toward malononitrile was reported when a product of proposed formula **272** was isolated [86ZN(B)925].

The synthesis of macrocyclic 4*H*-pyrans **161** was realized in the following operations: Both 3-Br substituents in the 2,6-aryl groups of starting 4*H*-pyrans **103c** ($\text{R}^1 = \text{R}^2 = \text{H, Me}$) were replaced by lithium (with BuLi) and then by two CHO groups (with DMF and hydrolysis). Borohydride reduction of the dialdehydes gave the appropriate diols which afforded the macroheterocycles **161** with diethylene glycol ditosylate (86TL3183; 88JOC374).

2. Conversions Accompanied by Heterocyclizations

a. *Heterocyclizations of 2-Amino-4*H*-pyrans.* Push–pull molecular (Z)-fragments $\text{H}_2\text{NC}=\text{CCN}$ and $\text{H}_2\text{NC}=\text{CCO}_2\text{Et}$ in various 2-amino-4*H*-pyrans exhibit a considerable tendency to form additional side-chain heterocyclic rings. The agents used for this purpose are shown in Table XX.

Hydrazine hydrate caused the formation of fused pyrazole-like rings as found in the conversions shown in Scheme 10. The reagent was observed to react more rapidly with the fragment $\text{H}_2\text{NC}=\text{CCO}_2\text{Et}$ as found in the conversion of cyano ester **149b** to fused 2-amino-3-cyano-4*H*-pyran **45** ($\text{R}^1 = \text{CN}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Me}$, $\text{R}^4 = \text{H}$) [86ZN(B)925].

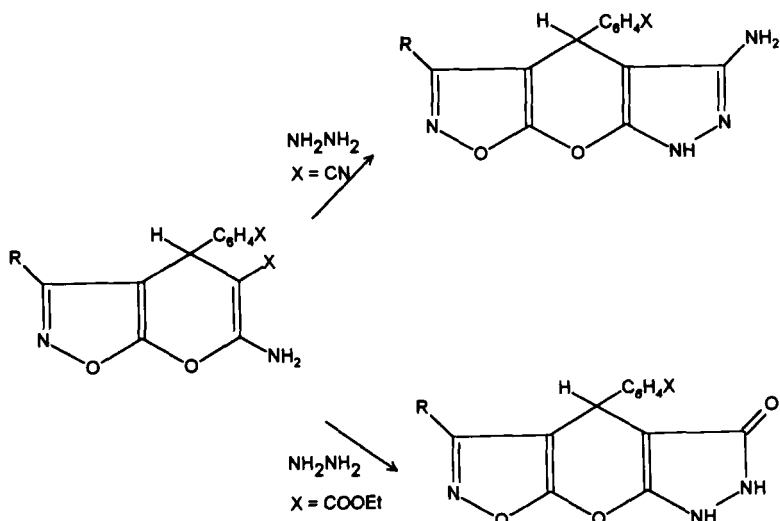
Pyranopyrimidine **273a** was prepared from 2-amino-3-ethoxycarbonyl derivative **150a** by heating with formamide [90IJC(B)1020], while analogous products **273b** and **273c** ($\text{R}^3 = 2\text{-furyl, 2-thienyl, 2-ClC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$) were obtained from 2-amino-3-cyano precursors **150b** (82RPQ133) and appropriately $\text{R}^1, \text{R}^2, \text{R}^3$ -substituted **165** (88AP131; 89LA585) with acetic anhydride. The same reagent converted carboxylic acid **150** ($\text{X} = \text{CO}_2\text{H}$) to oxa analog **273d** [90IJC(B)1020]. Similar products **274a, b** were reported to be formed by heterocyclization with some isothiocyanates—namely, $\text{150a} + \text{PhNCS} \rightarrow \text{274a}$ [91IJC(B)25] and $\text{149b} + \text{PhCONCS} \rightarrow \text{274b}$ [86ZN(B)925]. Similar tentative structures have been proposed for analogous reactions of PhCONCS with other 2-amino-3-cyano derivatives **165** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ac, CO}_2\text{Et}$; $\text{R}^3 = \text{Ph, 4-MeC}_6\text{H}_4, 2\text{-furyl, 2-thienyl}$) (87JHC1677; 88AP131).

TABLE XX
AGENTS USED FOR HETEROCYCLIZATIONS OF 2-AMINO-3X-4H-PYRANS

Agent	X	References	Agent	X	References
NH ₂ NH ₂ · H ₂ O	CN	82H2251	Cl ₃ CCN	CN	86ZN(B)925; 88AP131
NH ₂ NH ₂ · H ₂ O	CO ₂ Et	82H2251; 86ZN(B)925	Cl ₃ CCN	CO ₂ Et	91IJC(B)25
Ac ₂ O	CN	82RPQ133; 88AP131; 89LA585	CH ₂ (CN) ₂	CN	86ZN(B)925; 87JHC1677; 88AP131; 89APR201
Ac ₂ O	CO ₂ H	90IJC(B)1020	NCCH ₂ COPh	CN	89APR201
HCONH ₂	CO ₂ Et	90IJC(B)1020	NCCH ₂ CO ₂ Et	CN	86ZN(B)925; 88AP131; 89APR201
PhNCS	CN	87JHC1677; 86ZN(B)925; 88AP131	NCCH ₂ CO ₂ Et	CO ₂ Et	91IJC(B)25
PhNCS	CO ₂ Et	91IJC(B)25	R ¹ R ² C = CXY ^b	CN	86ZN(B)925
4-ArOCH ₂ COCl ^a	CO ₂ Et	90IJC(B)1020			

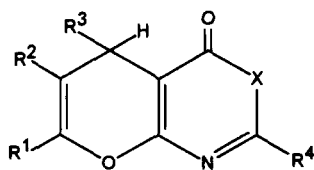
^a Ar = 4-O₂NC₆H₄.

^b R¹ = CCl₃, R² = NH₂, X = CN, and Y = CO₂Et.



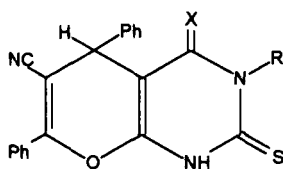
SCHEME 10

Pyranoaminopyrimidines **275a** ($\text{R}^3 = \text{Ph}$, 2-furyl, 2-thienyl) were obtained by the reaction of 2-amino-3-cyano-4*H*-pyrans **149b** [86ZN(B)-925] and corresponding **165** (88AP131) with Cl_3CCN -piperidine or

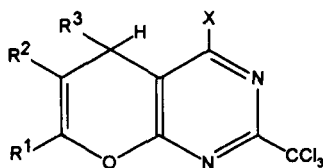


(273)

- (a) $\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{CN}$, $\text{R}^4 = \text{H}$, $\text{X} = \text{NH}$
 (b) $\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{CO}_2\text{Et}$, $\text{R}^4 = \text{Me}$, $\text{X} = \text{NH}$
 (c) $\text{R}^1 = \text{R}^4 = \text{Me}$, $\text{R}^2 = \text{CO}_2\text{Et}$, R^3 see text, $\text{X} = \text{NH}$
 (d) $\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{CN}$, $\text{R}^4 = \text{Me}$, $\text{X} = \text{O}$



- (274a) $\text{R} = \text{Ph}$, $\text{X} = \text{O}$
 (274b) $\text{R} = \text{PhCO}$, $\text{X} = \text{NH}$

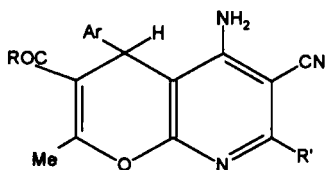


- (275a) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CO}_2\text{Et}$, R^3 see text, $\text{X} = \text{NH}_2$
 (275b) $\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{CN}$, $\text{X} = \text{OH}$

$\text{Cl}_3\text{CCN}-\text{Et}_3\text{N}$, respectively. The treatment of 2-amino-3-ethoxycarbonyl derivative **150a** with $\text{Cl}_3\text{CCN}-\text{EtOH}$ resulted, however, in hydroxypyrimidine product **275b** [91IJC(B)25].

Malononitrile and β -cyanocarbonyl compounds have been observed to heterocyclize with 2-amino-3-cyano-4*H*-pyrans to various pyranocyanopyridines or pyranocyanopyridones, respectively. Thus, $\text{CH}_2(\text{CN})_2$ in the presence of piperidine or Et_3N reacted with **149b** or similarly substituted **165**, affording fused diaminocyanopyridines **276a** [86ZN(B)925; 87JHC1677; 88AP131]. Similarly, the heterocyclizations of anilides **165** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{PhNHCO}$; $\text{R}^3 = \text{Ph}$, 4- ClC_6H_4 , 4- MeC_6H_4 , 4- MeOC_6H_4 , 4- $\text{O}_2\text{NC}_6\text{H}_4$) gave analogous products **276b** ($\text{Ar} = \text{R}^3$). However, other suggestions regarding more complex product structures (89APR201) should be considered with caution because of limited spectral data.

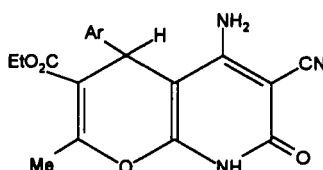
Heterocyclizations of 4*H*-pyrans **149a** and appropriately substituted **165** with ethyl cyanoacetate under similar conditions gave the corresponding pyranopyridones **277a** [86ZN(B)925; 89APR201] and **277b** (88AP131). The reaction with the fragment $\text{H}_2\text{NC}=\text{CCO}_2\text{Et}$ in **150a** proceeded differently, however, leading to pyranopyrimidine **278** [91IJC(B)25]. A similar structure proposed for the product from 2-amino-3-cyano-4*H*-pyran **149b** and $\text{Cl}_3\text{C}(\text{NH}_2)=\text{C}(\text{CN})\text{CO}_2\text{Et}$ [86ZN(B)925] requires further confirmation.



(276a) Ar = Ph, 4- MeC_6H_4 , 2-furyl, 2-thienyl;

R = EtO; R' = NH₂

(276b) Ar see text, R = PhNH, R' = Ph

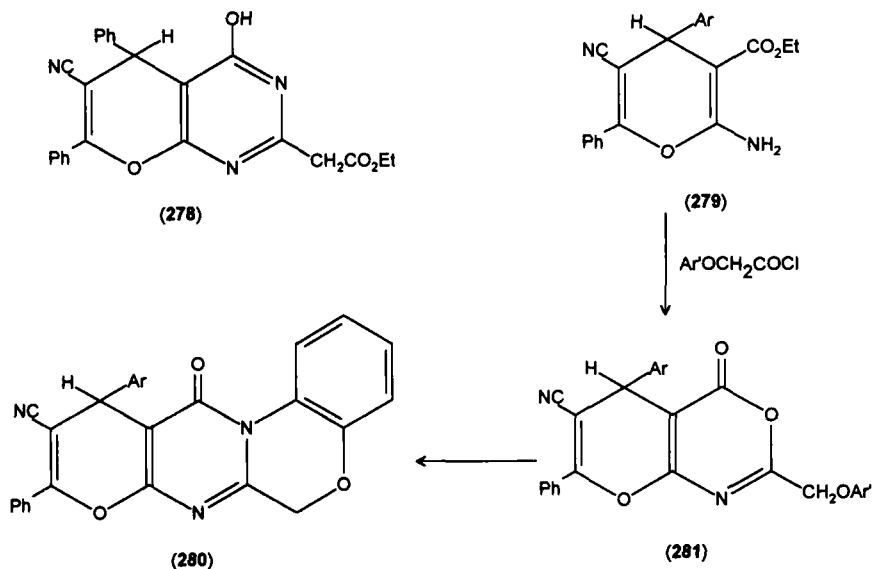


(277a) Ar = Ph, 4- XC_6H_4 (X: Cl, Me, MeO, NO₂)

(277b) Ar = 2-furyl, 2-thienyl

A novel heterocyclic ring closure has been reported in the reaction of 4*H*-pyran **279** with 4- $\text{O}_2\text{NC}_6\text{H}_5\text{OCH}_2\text{COCl}$, initially affording pyranooxazolinone **281** (66%) and finally a more complex annulated 4*H*-pyran derivative **280** [90IJC(B)1020]; see Scheme 11.

b. Intramolecular Heterocyclic Ring Closures. A Claisen-type condensation of *N*-acylamino-2-ethoxycarbonyl derivatives **266c,d** to cyanodiones **282a,b** was realized by heating the starting substances with NaH in toluene. Other oligocyclic structures also have been considered for products obtained at higher temperatures [91IJC(B)25].

SCHEME 11 (Ar = 2-O₂NC₆H₄, Ar' = 4-O₂NC₆H₄)

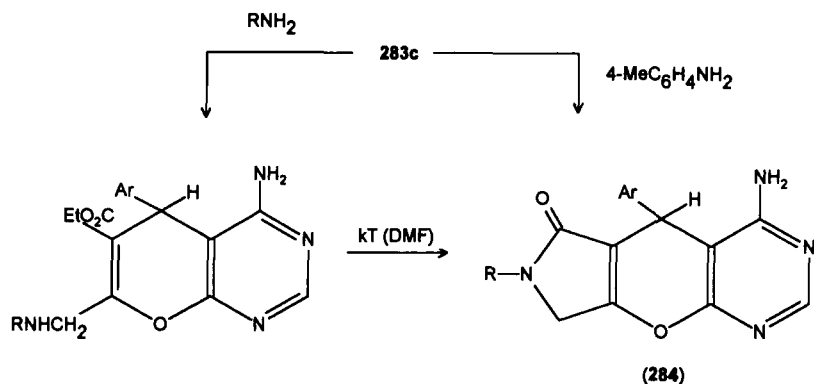
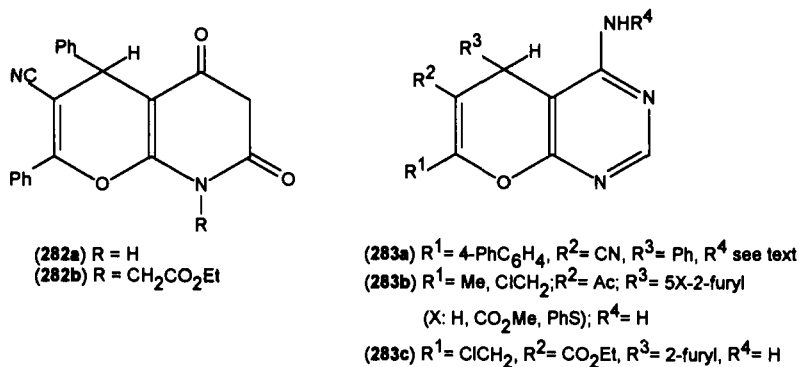
2-(*N*-Ethoxymethylene)amino derivative **267a** (X = EtO) was converted with ammonia, hydrazine hydrate, and primary amines to pyrano-pyrimidines **283a** (R⁴ = H, NH₂, Me, Et, Pr, Bu, PhCH₂) (84CCC2309). Analogous products **283b,c** were prepared by heating the corresponding amidines **267b** (X = NH₂) in EtOH (88SOC399; 89CCC1336; 89M1101). This cyclization combined with a nucleophilic side-chain substitution was exploited for the synthesis of more complex 4*H*-pyrans **284** (89CCC1336), as shown in Scheme 12. Similar side-chain substitution was used in the synthesis of other oligocyclic derivatives **285** from *N*-acyl derivative **265** (R¹ = R³ = Ph, R² = CN, R⁴ = 2-pyridylNHCO, R⁵ = ClCH₂) according to Scheme 13 [90IJC(B)1020].

I. CYCLOADDITION REACTIONS

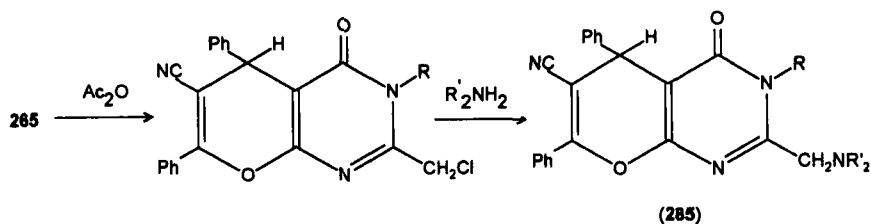
Several examples of the title conversion for the pyran ring have been reported in the last decade.

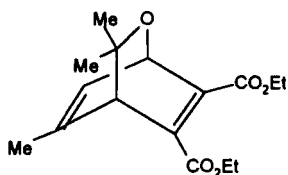
1. Cycloadditions of 2*H*-Pyrans

The formation of *endo*-peroxides from 2*H*-pyrans with singlet dioxygen was discussed in Section V.A.5. Cycloadduct **286** was apparently a

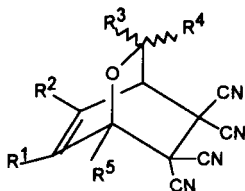
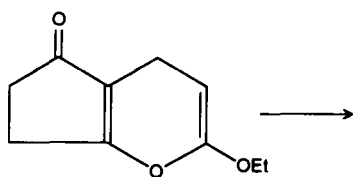
SCHEME 12. ($Ar \approx Ph$; $R = Bu, Ph, 4-MeC_6H_4, PhCH_2$)

key intermediate in the conversion of 2,2,4,6-tetramethyl-2*H*-pyran **107** ($R = R' = Me$) with DMAD to benzene derivative **236a** (83JA1263); see Section V.F.1. On the other hand, cycloadducts **287a,b** were isolated after the reactions of 2*H*-pyrans **76** (92TL883) and **127a** ($Ar = Ar' = Ph$, $R = Me$) with TCNE (83JPR729).

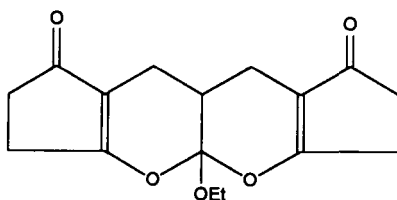
SCHEME 13. ($R = 2\text{-pyridyl}$, $R' = Me, Et$)



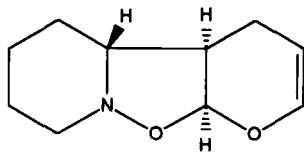
(286)

(287a) $R^1 = \text{CO}_2\text{Me}$, $R^2 = R^3 = R^4 = R^5 = \text{H}$ (287b) $R^1 = \text{H}$, $R^2 = R^3 = R^5 = \text{Ph}$, $R^4 = \text{H}$ 

(289)



(290)



(288)

2. Cycloadditions of 4H-Pyrans

1,3-Dipolar cycloaddition of unsubstituted 4-pyran **2** to 2,3,4,5-tetrahydropyridine-1-oxide gave $[2\pi + 2\pi]$ -cycloadduct **288** (70%) at 140°C [83CC654; 90JCS(P1)2593]. Unstable fused 2-ethoxy-4H-pyran **289** generated from $\text{HC}\equiv\text{COEt}$ and 2-methylene-1,3-cyclopentadione underwent subsequent $[2\pi + 2\pi]$ -cycloaddition to the second component, affording final cycloadduct **290** (88JOC4038). An unusual structure was found for cycloadduct (88CZ309; 90LA995) obtained by the reaction sequence shown in Scheme 14.

J. FORMATION OF METALLIC COMPLEXES

The Co-coordinated 2H-pyrans **61**, **63**, and **65–67** were prepared by ring-closure methods (89SL15; 89TL2893), (see Section III.C.1,

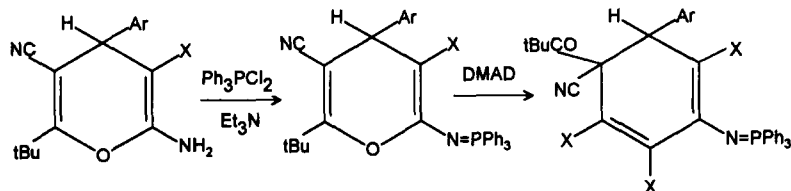
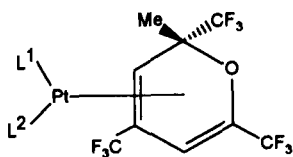
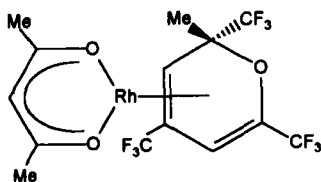
SCHEME 14. (Ar = 2-ClC₆H₄, X = CO₂Et)

Table VII), while Mn-coordinated 4*H*-pyrans **92** (R = *t*Bu, Ph; R' = C₅H₄Mn(CO)₃) were obtained from appropriate pyrylium salts (85KGS593); see Section IV.A.2. The new approaches to Mo-coordinated complexes of simple 2*H*-pyrans **138**, **190**, **191**, and **229–233** (90JA9660); 93JA891) were discussed in Sections IV.D.1, V.B.2, and V.E.3.

Earlier work on metal complexation of 2,4,6-trifluoromethyl-2-methyl-2*H*-pyran described the preparation of Pt-coordinated compounds **291** (L¹ = L² = PPh₃, *t*BuNC, 2,6-dimethylbenzonitrile; L¹ = C₂H₄, L² = PPh₃; L¹, L² = cycloocta-1,5-diene) and Rh-complex **292**. While the η² mode of attachment of the pyran ring to Pt was established in **291**, Rh in **292** was found to be η⁴-coordinated [80JCS(D)2095]. Some other Pt-complexes containing 2*H*-pyran carbene-like ligands were also investigated [87OM63].

Bond energies of 4*H*-pyran crowns **162** with alkali metal ions (Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺) have been established (88JOC374).

(291) L¹, L² see text

(292)

K. OTHER TRANSFORMATIONS

A 4,4'-linkage between crown components **161** and **162** (R = Me) via a—CH=CH—bridge was reported to be achieved by treatment with *ortho*-ester (EtO)₃CH (88JOC374).

VI. Physical Properties and Theoretical Chemistry

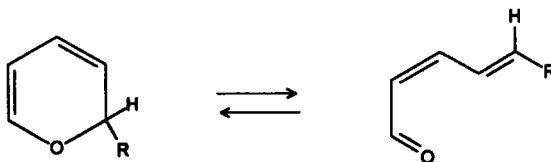
A. MOLECULAR ENERGY AND ELECTRONIC STRUCTURE

A number of experimental results have shown that the stability of *2H*-pyrans is limited by their valence-bond tautomerism (see Section V.C.1). Semiempirical quantum-chemical methods CNDO/2 and MNDO (83CCC1007), MINDO/3 and MNDO (84JPR955), and MNDO (87CCC399) as well as nonempirical *ab initio* Mo procedures using STO-3G, 4-31G (83CCC1007; 87CCC399), and 3-21G (90CCC10) basis sets were successfully applied to the interpretation of substituent effects in tautomeric equilibria. A key factor was found to be the ability of a given open-chain tautomer to adopt a planar geometry (conformation). In such cases the equilibria are shifted in favor of dienones.

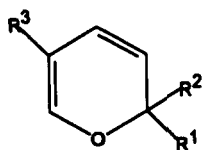
In connection with the well-known spiropyran photochromism, several semiempirical MO studies of the reversible interconversion of *2H*-pyrans to isomeric 2,4-dienones (Scheme 15) were employed as model calculations to elucidate substituent effects in **293a–d** on equilibria in the S_0 , S_1 , and T_1 states [82KGS1028; 84KGS747; 84JCS(F2)1513; 88KGS172; 88ZFK1077; 91KGS310]. Although the results of these model calculations qualitatively agree with the experimental data, the general application of such approximation methods should be taken with caution, especially in the case of conjugated systems in the ground and excited states.

The AM1 calculations performed for 2,2'-bis-*2H*-pyrans **294** were used as approximate MO models of thermo- and piezochromic benzo effects to establish X-substituent effects on solid-state properties. The radicals formed by the 2,2'-homolysis of **294**-like molecules have been proposed to be colored species. Molecular orbital calculations have suggested very slight electronic effects but an important steric substituent effect on the C(2)—C(2') bond length [92JCS(P2)59].

Nonempirical MO calculations were also used to predict the IR absorption spectrum of unsubstituted *2H*-pyran (**1**) (90CCC10). Some MNDO and AM1 studies were carried out to obtain a thermodynamic interpretation of the regioselectivity of the formation of pyrans from pyrylium cations



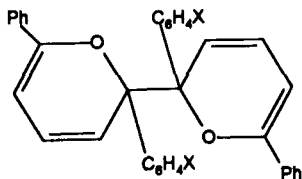
SCHEME 15.



(293)

- (a) $R^1 = \text{H}, \text{NH}_2; R^2 = R^3 = \text{H}$
 (b) $R^1 = R^2 = \text{H}, R^3 = \text{OH}, \text{NH}_2, \text{NO}_2, \text{CHO}$
 (c) $R^1 = \text{OH}; R^2 = \text{H}, \text{NH}_2; R^3 = \text{H}$
 (d) $R^1 = \text{OH}, \text{NH}_2; R^2 = \text{H}; R^3 = \text{H}, \text{CHO}$

(92JOC4431). The results indicated that the 2*H*-isomers are significantly stabilized by a generalized anomeric effect when the 2-substituent is OCH_3 . Charge distributions and orbital interactions analyzed by the EHT methods were successfully used for investigations on the reactions of substituted pyrylium ions with azide as a nucleophile (84T3549). The higher relative energy of 4*H*-pyran **1** in comparison to its 2*H*-isomer **2** has been repeatedly indicated by *ab initio* MO calculations when the STO-3G, 3-21G, 4-31G, and 6-31G* basis sets were used (90JST261). The effect of 4-substitution was also discussed (90JST261).



(294) X = 4-Me, 4-Cl, 4-OH, 4-CN

The molecular and electronic structure of 4*H*-pyran **2** and its 4-oxo and 4-thioxo derivatives was studied by the MNDO method to establish the preferred site of protonation at the exo-heteroatom in accordance with experimental findings [84ZN(A)267]. The molecular geometries agreed semiquantitatively with the experimental data. The MNDO method has been also successful in predicting fragmentation patterns in methyl- or ethyl-substituted 2*H*- and 4*H*-pyrans. The main fragmentation processes were hydrogen or alkyl eliminations leading to the corresponding pyrylium cations (83IJM399; 86OMS459).

Both AM1 and force-field calculations of 4-methyl-4*H*-pyran and 4-methylcoumarin anion were employed as approximate models for a transition-state study of the alkaloid-induced enantioselective electroreduction of 4-methylcoumarin (93LA609).

B. ELECTRONIC SPECTRA

The use of UV spectra for the elucidation of the structure of substituted pyrans has been limited because of much spectral band overlapping. In the case of conjugation with substituents, the characteristic bands have been observed to be bathochromically shifted. *2H*-Pyrans as a rule exhibited longer-wavelength absorptions in comparison with similarly substituted *4H*-pyrans. Representative spectral data are shown in Table XXI.

In addition to various kinetic and equilibria measurements, typical applications of UV-VIS spectra have been, employed in systematic investigations of photocoloration and related photochemistry of 2,4,4,6-tetraaryl-*4H*-pyrans **8** [91JPP(A)345; 92JCS(P2)1301] as well as 2-benzyl- and 2-methyl-2,4,6,-triphenyl-*2H*-pyrans (86JP187).

Ultraviolet spectrophotometry was also used to monitor valence-bond isomerizations of various *2H*-pyrans (see Section V.C.1) in solvent-effect investigations (85IZV1075; 87IZV821; 88KGS1325) and to demonstrate the site of methoxide-ion attachment to pyrylium cations [86JOC4385; 89JCS(P2)1393].

UV-VIS measurements were also used to study the reversible coupling of the corresponding pyranil radicals to 4-4'-bis-*4H*-pyran **96** (86NJC345; 86TL4489; 89BCJ2279; 89RC157).

C. NUCLEAR MAGNETIC RESONANCE

Almost all experimental work on pyrans has employed ^1H and ^{13}C NMR spectra. However, detailed assignments of all the measured signals are still rare [85MRC793; 92JCS(P2)1301]. Typical spectral data for representative *2H*- and *4H*-pyrans are given in Tables XXII to XXV. Carbon-13 chemical shifts were used to study the transmission of substituent effects when applied to the classical Hammett equation (90MR212).

D. INFRARED SPECTRA

Infrared absorption spectra have frequently been used as an additional item in structure proofs of *2H*- and *4H*-pyran rings. Identification of functional groups is the most important application. Assignments of the bands belonging to the heterocyclic ring have not been common and are largely tentative. Higher wave numbers have been repeatedly observed to characterize *4H*-isomers. Assignments of IR and Raman spectra of *4H*-pyran **2** (93JA8396) and various substituted 2-amino-*4H*-pyrans **295** (87JST19;

TABLE XXI
ELECTRONIC ABSORPTION SPECTRA OF SOME 2*H*-PYRANS DERIVATIVES

Substituent at position					λ max	log ϵ	References
2	3	4	5	6			
Ph	H	Ph, Ph	H	Ph	259	4.36	91JPP(A)345
PH	H	Ph, <i>p</i> -Br-Ph	H	Ph	253	4.54	91JPP(A)345
<i>p</i> -Br-Ph	H	Ph, Ph	H	<i>p</i> -Br-Ph	255	4.59	91JPP(A)345
Me ₂ N, H	Br	H	COOMe	Me	236, 304	17,250, 10,350 ^a	89IZV1323
Me ₂ N, H	OEt	H	COOMe	Me	230, 300	9461, 6426 ^a	89IZV1323
Me ₂ N, H	<i>i</i> Pr	H	COOMe	Me	232, 283	9715, 6600 ^a	88KGS1325
Me ₂ N, Ph	Me	Ph	H	Ph	240, 343	4.28, 4.02	84JPR657
Me ₂ N, Ph	Me	Ph	Me	Ph	328	3.90	84JPR657
NH ₂	CN	H, 2-furyl	COOEt	CH ₂ Cl	230, 286	3.42, 2.44	83CCC1336
NH ₂	CN	H, Ph	CN	4-biphenyl	243, 297	4.19, 4.32	83CCC3123
Me	COMe	H, Ph	H	2-OH-4-MeO-Ph	208, 274	4.43, 4.21	83H2369

^a ϵ value.

TABLE XXII
¹H NMR DATA FOR SOME 2*H*-PYRAN DERIVATIVES

Position/Substituent					References
2	3	4	5	6	
2.43s, 7.00–7.77m NMe ₂ , Ph	1.53s Me	7.00–7.77m Ph	5.76s H	7.00–7.77m Ph	84JPR657
2.41s, 5.63 NMe ₂ , H	— Br	7.01 H	3.66 COOMe	2.3 Me	89IZV1323
3.29s MeO, Ph	1.41s Me	7.04–7.64m Ph	5.91s H	7.04–7.64m Ph	83JPR729
3.42s MeO, Ph	6.58–7.79m Ph	6.58–7.79m Ph	6.21s H	6.58–7.79m Ph	83JPR729
1.06s <i>t</i> Bu, <i>t</i> Bu	5.21d H	5.77dd H	4.60d H	1.74s Me	91CB2633
5.23s MeO, H	2.24s Me	— COOEt	6.64s H	— CN	91CB1425
1.48s Me, Me	5.78d ^a H	— Cl	5.30d ^a H	7.35–7.65m Ph	91HCA27
2.38, 5.36 NMe ₂ , H	1.31, 3.86 OEt	5.73 H	3.71 COOMe	2.3 Me	89IZV1323

^a Tentative assignment.

88JST63) have been discussed in detail. Some skeletal absorption maxima for various 2*H*- and 4*H*-pyrans are given in Table XXVI.

E. X-RAY CRYSTALLOGRAPHY AND MOLECULAR STRUCTURE

X-ray structure determinations were performed for the following pyrans:

2,4,4,6-tetraphenyl-4*H*-pyran [90AX(C)1727],
 3,5-dicyano-2,6-dimethyl-4-phenyl-4*H*-pyran [87AX(C)1430],
 2-amino-5-cyano-3-ethoxycarbonyl-4,6-diphenyl-4*H*-pyran (88JST63),
 2-amino-3,5-dicyano-4-isopropyl-4-methyl-4*H*-pyran (87JST19),

TABLE XXIII
¹H NMR DATA FOR SOME 4*H*-PYRAN DERIVATIVES

Position/Substituent					References
2	3	4	5	6	
7.41–7.70m <i>p</i> - <i>t</i> Bu–Ph	5.72s H	7.28–7.34m Ph, Ph	5.72s H	7.41–7.70m <i>p</i> - <i>t</i> Bu–Ph	92JCS(P2)1301
3.61s MeO	1.53s Me	2.60–2.73m H, H	4.64–4.87m H	6.16–6.33m H	89JOC2736
3.59s Meo	3.54–3.81m H	2.74–3.24m, 1.08d H, Me	4.54–4.88m H	6.11–6.31m H	83JOC2736
3.58s MeO	3.55–3.82m H	2.64–2.91m H, H	4.43–4.66m H	1.76s Me	83JOC2736
3.62s MeO	1.52s Me	1.56–2.72m H, H	4.42–4.58m H	1.76s Me	83JOC2736
7.39s H	9.34s CHO	4.73s H, Ph	9.34s CHO	7.39s H	85LA1987
7.17–7.30m H	9.31s CHO	4.89s H, <i>p</i> -Cl–Ph	2.35s MeCO	2.11s Me	87CCC2687
7.23s H	9.38s CHO	4.90s H, 3-thienyl	4.10q, 1.17t EtOCO	— ^a Me	87CCC2687

^a Not given.

2-amino-6-chloromethyl-3-cyano-5-ethoxycarbonyl-4-(2-furyl)-4*H*-pyran [90AX(C)788], and fused 4*H*-pyran derivative **296** (86ZOR1315).

The absolute configuration at carbon C(4) in optically active 4*H*-pyrans **42** (R = Me, R' = MeO; R = Ph, R' = EtO) was also determined (92TL3809; 93T7133).

The structures of Mo-, Co-, and Pt-coordinated π -complexes of various 2*H*-pyrans were also determined [80JCS(D)2095; 89TL2893; 90JA9660]. Structures of the pyran ligands exhibited features similar to those of free heterocycles, i.e., nearly planar arrangements possessing a slight deviation of the centers O(1) and C(4) from the plane passing through the C(2), C(3), C(5), and C(6) atoms. In the case of fused 4*H*-pyran **296**, the cyclohexene ring had a half-chair conformation (86ZOR1315).

TABLE XXIV
¹³C NMR DATA FOR SOME 2*H*-PYRAN DERIVATIVES

Position/Substituent					References
2	3	4	5	6	
98.62 NMe ₂ , H	104.14 Br	127.88 H	103.34 COOMe	168.43 Me	89IZV1323
104.2 <i>s</i> BuNH ₂ , 4-SO ₃ H-Ph	113.5 H	136.8 4-MeO-3-SO ₃ H-Ph	93.0 H	147.1 4-SO ₃ H-Ph	84JCS(P2)849
89.5 <i>t</i> Bu, <i>t</i> Bu	116.0 ^a H	120.3 ^a H	93.0 H	153.9 Me	91CB2633
100.54 MeO, H	120.84 ^a Me	123.09 ^a COOEt	113.67 H	138.52 CN	91CB1425
91.31 NMe ₂ , H	142.53 OEt	93.61 H	101.02 COOMe	160.5 Me	89IZV1323

^a The assignment of the signal 3–4 may be interchanged.

F. OTHER SPECTROSCOPIC TECHNIQUES

Mass spectral measurements have been used to establish the parent molecular mass. Detailed studies of fragmentation patterns have not yet become common. Typical fragmentations gave mainly the ionic species (M-1)⁺ and some others due to elimination of various substituents.

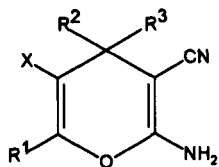
The most abundant species in the fragmentations are the considerably stable pyrylium cations (83CCC3123; 83IJM399; 87CP623). These species have also been found frequently in the mass spectra of substituted furans owing to rearrangements of primary radical cations (84CR163; 84TL3815; 86NJC79; 86OMS445).

2,2-Dimethyl-2*H*-pyranyl radical ion and 2-methylpyrylium ion also were found among the products of intracluster polymerization reactions of acetylene and acetone (91JPC9625). Mass spectrometric fragmentations of 2,6-diaryl-4,4-diphenyl-4*H*-pyrans **8** have also been investigated in detail (87CP623).

Electron spin resonance spectra were successfully used to identify radicals formed by oxidations and reductions of 4*H*-pyrans and pyrylium salts. These radicals were generated chemically, electrochemically,

TABLE XXV
¹³C NMR DATA FOR SOME 4*H*-PYRAN DERIVATIVES

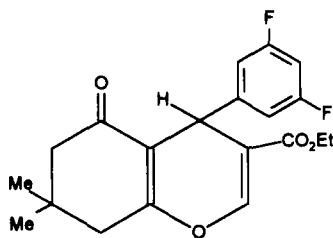
Position/Substituent					References
2	3	4	5	6	
141.37 Ph	104.89 Br	60.15 Ph, Ph	104.89 Br	141.37 Ph	92CCC546
147.04 <i>p</i> - <i>t</i> Bu-Ph	103.44 H	47.35 Ph, Ph	103.44 H	147.04 <i>p</i> - <i>t</i> Bu-Ph	92JCS(P2)1301
159.53 NH ₂	53.88 CN	32.64 2-furyl, H	108.44 COOEt	154.22 CH ₂ Cl	89CCC1336
160.1 NH ₂	57.8 CN	45.0 Ph, H	116.4 Ph	144.4 Ph	85MRC793
158.2 NH ₂	61.4 CN	32.4 Me, Me	94.0 CN	156.9 Ph	85MRC793
159.8 Me	89.2 CN	38.5 Ph, H	89.2 H	159.8 CN	85MRC793
159.2 HN ₂	55.6 CN	38.7 Ph, H	90.1 CN	158.2 Me	85MRC793
155.9 H	123.8 CHO	31.8 Ph, H	123.8 CHO	155.9 H	85LA1987
159.6 NH ₂	54.5 CN	32.6 2-furyl, H	113.0 MeCO	155.9 Me	90CCC718



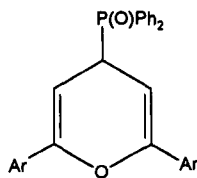
(295) R¹ = H, Me, Ph; R² = H, Et; R³ = Me, *i*Pr, *s*Bu, Ph;
 X = Ph, CN, Ac, COOEt

TABLE XXVI
 IR DATA FOR SOME 2*H*- AND 4*H*-PYRANS

	$\nu_{C=C}$	References
2-Dimethylamino-3-methyl-2,4,6-triphenyl-2 <i>H</i> -pyran	1660	84JPR657
3-Methyl-2-piperidino-2,4,6-triphenyl-2 <i>H</i> -pyran	1650	84JPR657
2-Dimethylamino-2-(4-methoxyphenyl)-3-methyl-4,6-diphenyl-2 <i>H</i> -pyran	1650	84JPR657
3,5-Dimethyl-2-dimethylamino-2,4,6-triphenyl-2 <i>H</i> -pyran	1647	84JPR657
Ethyl 6-cyano-2-methoxy-3-methyl-2 <i>H</i> -pyran-4-carboxylate	1640	91CB1425
2,2-Bis(1,1-dimethylethyl)-6-methyl-2 <i>H</i> -pyran	1600,1660	91CB2633
5-Acetyl-4-(4-chlorophenyl)-6-methyl-4 <i>H</i> -pyran-3-carbaldehyde	1596,1665	87CCC2687
4 <i>H</i> -Pyran-2,6-dicarboxylic acid	1642,1687	87CJC704
4- <i>p</i> -Tolyl-2,4,6-trimethyl-4 <i>H</i> -pyran	1710	87H1495
1-[6-(2-Hydroxy-4-methoxyphenyl)-2-methyl-4-phenyl-4 <i>H</i> -pyran-3-yl]ethanone	1590,1620	83H2369
6-(4-Biphenyl)-2-ethoxymethyleneamino-4-phenyl-3,5-dicyano-4 <i>H</i> -pyran	1622,1670	84CCC2309
2-Amino-5-cyano-3-ethoxycarbonyl-4,6-diphenyl-4 <i>H</i> -pyran	1630	82M53
2-Acetylamino-5-cyano-3-ethoxycarbonyl-4,6-diphenyl-4 <i>H</i> -pyran	1610,1650	82M53
2-Phenyl-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4 <i>H</i> -chromene	1625,1680	82ZOR2184
2,4,4,6-Tetraphenyl-4 <i>H</i> -pyran	1640,1687	87CP623
2-Amino-3,5-dicyano-4-isopropyl-6-methyl-4 <i>H</i> -pyran	1598,1648,16	87JST19
2-Amino-3-cyano-4,5,6-triphenyl-4 <i>H</i> -pyran	1605,1652,1683	87JST19
2,6-Dimethyl-3,5-dicyano-4-phenyl-4 <i>H</i> -pyran	1685	88JST63
2,4,6-Triphenyl-4- <i>p</i> -tolyl-4 <i>H</i> -pyran	1680	89CCC1854
4 <i>H</i> -Pyran	1634,1694	93JA8396



(296)

(297) Ar = Ph, 4-MeOC₆H₄

and photochemically [83AJC1983; 83ZOB606; 84JP131; 84ZNP136; 85BCJ2600; 85SA(A)955; 85ZOB2136; 86DOK998; 86NJC345; 86TEK741; 87VB29; 89BCJ2279; 89RCI57; 83ZOB606; 91KGS47]. Hyperfine splitting constant analysis was applied to analyze spin densities in the π -system of **297** (90ZOB1012).

Electron transmission spectroscopy has been employed to locate the temporary anion states associated with electron capture into the empty π^* -MOs of 4*H*-pyran and 4-pyrone (86CPL375).

Nanosecond and microsecond laser flash spectroscopy was employed to identify a photophysical path in the photochemistry of 2-methyl- and 2-benzyl-2,4,6-triphenyl-2*H*-pyrans (86JP187).

G. MISCELLANEOUS

Electrochemical measurements (cyclic voltammetry, polarography) were carried out to explain the electrochemical behavior of pyrans and pyrylium salts (83ZOB606; 84JP131; 86AJC865; 86NJC345; 86ZOB863; 87AJC579; 88OM1122; 88OM1131; 90ZOB1012; 91KGS900). Pyrylium salts have been shown to be the most resistant toward electrochemical reduction in comparison to their S- and Se-analogs (86ZOB863; 86ZOB863).

2*H*-Pyran **1** was considered to originate from acrolein and $\text{H}_2\text{C}=\text{CHOBu}$ in a computational study of free connection due to homogeneous, arbitrary-order reactions (86TOK616). A computer-assisted prediction of the normal boiling points of pyrans has been reported (92JCI306).

VII. Other Properties

2*H*-Pyran **81a** ($\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$) is a component of volatile constituents of *Michelia champaca* L. (91JE129). Unstable 4-hydroxy-3-hydroxymethyl-4*H*-pyran is a component of antibiotics in *Rhizoctania solani* (84NSB263). The 2-methyl derivative of fused 4*H*-pyran **22b** was isolated after photolysis of a cannabinol material (92M93). Formation of a 2-methoxypyran during thermal decomposition of rice hulls was followed kinetically (91KD86).

A perfluoroisopentylpyran was tested as a vehicle for administering therapeutic drugs (83EUP91313). 2-Amino-3-cyano-4*H*-pyran **295** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = 3\text{-O}_2\text{NC}_6\text{H}_4$, $\text{R}^3 = \text{H}$, $\text{X} = \text{CO}_2\text{Et}$) and its 3,5-diester were tested as antibodies to dihydropyridine calcium entry blockers (86BP4479). Complex 4*H*-pyran 3,5-diester **53c** did not exhibit antihypertensive activity

(85CPB3787). 4*H*-Pyran-2,6-dicarboxylic acid is a weak inhibitor of tetrahydrodipicolinate *N*-succinyl transferase (86JBC6160).

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The Chemistry of Dithiadiazolylium and Dithiadiazolyl Rings*

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Foreword	140
A. List of Compounds	141
I. Introduction: Dithiadiazolyls, New Members of an Old Class of Free Radicals	142
II. Synthetic Approaches to the 1,2,3,5-Dithiadiazolylium Cation	146
A. Thiaryl Chloride as a Building Block in Sulfur–Nitrogen Chemistry	146
1. Ring-Retention Reactions of (NSCl) ₃	146
2. Use of (NSCl) ₃ in Ring-Expansion Reactions	147
3. Use of (NSCl) ₃ in Chain Formation	147
4. (NSCl) ₃ in Chain Expansion	148
5. (NSCl) ₃ in Heterocyclic-Ring Formation	148
B. Reaction of Nitriles with (NSCl) ₃	148
C. Reaction of Amidines and Amidinium Salts with SCl ₂	150
D. Other Routes to the 1,2,3,5-Dithiadiazolylium Ring System	152
1. From Toluene, NH ₄ Cl, and SCl ₂	152
2. From Tetrachloroethylene and (NSCl) ₃	152
3. From Aldazines and (NSCl) ₃	153
4. From Trichloroacetic Anhydride and (NSCl) ₃	153
5. Preparation of [X.CN [−] SSN] ⁺ Salts	153
E. Conclusions	154
III. Theoretical Studies of 1,2,3,5-Dithiadiazolylium Heterocycles	154
IV. Physical Properties of Mono-1,2,3,5-dithiadiazolylium Salts	158
A. Multinuclear Nuclear Magnetic Resonance Spectra	158
B. UV/Visible Spectra	159
C. Electrochemical Studies	161
D. Electron Spin Resonance Spectra	162
V. X-Ray Diffraction Studies of Mono-1,2,3,5-dithiadiazolylium Salts	162
A. 1,2,3,5-Dithiadiazolylium Salts of Hard Anions	163
B. 1,2,3,5-Dithiadiazolylium Salts with Anions That Interact In-Plane	163
C. 1,2,3,5-Dithiadiazolylium Salts with Anions That Interact Out-of-Plane	165

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D.	1,2,3,5-Dithiadiazolylium Salts Containing Both In-Plane and Out-of-Plane Anions	168
E.	Partially Reduced 1,2,3,5-Dithiadiazolylium Salts	168
VI.	Reactions of 1,2,3,5-Dithiadiazolylium Salts	170
A.	Metathesis and Addition Reactions	170
B.	Hydrolysis	171
C.	Reaction with a Nitrogen Plasma	171
VII.	Preparation of 1,2,3,5-Dithiadiazolylium Salts	174
A.	Disproportionation of 1,2,3,5-Dithiadiazolylium Salts	174
B.	Reduction of 1,2,3,5-Dithiadiazolylium Salts	174
C.	Rearrangement of 1,3,2,4-Dithiadiazolyl Radicals	175
VIII.	Theoretical Studies of 1,2,3,5-Dithiadiazolyl Radicals	175
IX.	Physical Properties of 1,2,3,5-Dithiadiazolyl Radicals	177
A.	Electron Spin Resonance Spectra	177
B.	Photoelectron Spectra	179
C.	Conductivity	179
D.	Magnetism	182
X.	Electron and X-Ray Diffraction Studies of 1,2,3,5-Dithiadiazolyl Radicals	183
A.	Electron Diffraction Studies	183
B.	X-Ray Diffraction Studies	183
1.	Twisted Configurations	183
2.	Cis-oid Configurations	185
3.	Trans-oid Configurations	188
4.	Monomeric Radicals	189
XI.	Reactivity of 1,2,3,5-Dithiadiazolyl Radicals	189
A.	Oxidation of Dithiadiazolyl Radicals	189
1.	Radical Coupling Reactions	190
2.	Radical-Trapping Reactions	191
B.	Reaction with a Nitrogen Plasma	192
C.	Reaction with Transition Metal Complexes	192
XII.	Preparation of Mono-1,3,2,4-dithiadiazolylium Salts	195
A.	[SNS][AsF ₆] as a Building Block in Sulfur-Nitrogen Chemistry	195
1.	Preparation of [SNS][AsF ₆]	195
2.	Reaction of [SNS][AsF ₆] with Alkynes	196
3.	Reaction of [SNS][AsF ₆] with Alkenes	197
4.	Reaction of [SNS][AsF ₆] with Phosphaalkynes	197
5.	Reaction of [SNS][AsF ₆] with Inorganic Reagents	197
B.	Reaction of Nitriles with [SNS][AsF ₆]	198
C.	From Thioacetamides and NSCl ₃	200
D.	Reaction of S ₄ N ₄ with Br ₂ in CS ₂	201
E.	By Ring Transfer	201
XIII.	Theoretical Studies of 1,3,2,4-Dithiadiazolylium Salts	201
XIV.	Physical Properties of 1,3,2,4-Dithiadiazolylium Salts	202
A.	Multinuclear Nuclear Magnetic Resonance Spectra	202
B.	Electrochemical Studies	204
C.	1,3,2,4-Dithiadiazolylium Salts as Host Lattices for S ₃ N ₂ ⁺ Radicals	204
XV.	X-Ray Diffraction Studies of 1,3,2,4-Dithiadiazolylium Salts	205
XVI.	Reactivity of 1,3,2,4-Dithiadiazolylium Salts	206
A.	1,3,2,4-Dithiadiazolylium Salts as Cationic Initiators for the Polymerization of THF	206

B. Reduction of 1,3,2,4-Dithiadiazolylium Salts	207
C. Metathesis	208
D. Hydrolysis	208
XVII. Preparation of 1,3,2,4-Dithiadiazolyls	209
A. By Reduction of 1,3,2,4-Dithiadiazolylium Salts	209
B. Preparation of Nonradical Dithiadiazolyls	209
1. Condensation of Chlorosulfonyl Chlorides with Silylated Sulfur Diimides	209
2. From $[\text{Me}_2\text{SnNSNS}]_2$ and a Halide	210
3. From a Cyano Anion and $[\text{SNS}][\text{AsF}_6]$	210
XVIII. Physical Properties of 1,3,2,4-Dithiadiazolyls	210
A. Electron Spin Resonance Spectra	210
B. Magnetic Data	213
XIX. Theoretical Studies of 1,3,2,4-Dithiadiazoyl Radicals	213
XX. X-Ray Diffraction Studies of 1,3,2,4-Dithiadiazolyls	214
XXI. Reactivity of 1,3,2,4-Dithiadiazolyls	216
A. Reactivity of 1,3,2,4-Dithiadiazoyl Radicals	216
1. Rearrangement	216
2. Polymerization	217
B. Reactivity of Nonradical 1,3,2,4-Dithiadiazolyls	218
1. Adduct Formation	218
2. Alkylation	218
XXII. Multi-1,2,3,5-dithiadiazolylium Salts and Dithiadiazolyls	219
A. Preparation of Multi-1,2,3,5-dithiadiazolylium Salts	219
1. Reaction of Amidines with SCl_2	220
2. Reaction of Nitriles with Ammonium Chloride and SCl_2	220
B. Chemical and Physical Properties of Multi-1,2,3,5-dithiadiazolylium Salts	221
1. Anion Metathesis Reactions	221
2. Electrochemical Studies	221
C. X-Ray Diffraction Studies of Multi-1,2,3,5-dithiadiazolylium Salts	222
D. Preparation of Multi-1,2,3,5-dithiadiazoyl Radicals	222
E. X-Ray Diffraction Studies of Multi-1,2,3,5-dithiadiazoyl Radicals	223
F. Physical Properties of Multi-1,2,3,5-dithiadiazoyl Radicals	223
1. Electron Spin Resonance Spectra	223
2. Magnetic Susceptibility	226
3. Conductivity	227
XXIII. Multi-1,3,2,4-dithiadiazolylium Salts and Dithiadiazolyls	227
A. Preparation of Multi-1,3,2,4-dithiadiazolylium Salts	227
B. Chemical and Physical Properties of Multi-1,3,2,4-dithiadiazolylium Salts	228
1. As Cationic Initiators for the Polymerization of THF	228
2. Metathesis and Addition Reactions	228
3. Electrochemical Studies	229
C. X-Ray Diffraction Studies of Multi-1,3,2,4-dithiadiazolylium Salts	229
D. Preparation of Multi-1,3,2,4-dithiadiazoyl Radicals	229
E. X-Ray Diffraction Studies of Multi-1,3,2,4-dithiadiazoyl Radicals	232
F. Physical Properties of Multi-1,3,2,4-dithiadiazoyl Radicals	233

1. Electron Spin Resonance Spectra	233
2. Electronic Properties	233
G. Reactivity of Multi-1,3,2,4-dithiadiazolyl Radicals	235
1. Oxidation	235
2. Solution Rearrangement	235
3. Solid-State Rearrangement	235
XXIV. Mixed 1,3,2,4-/1,2,3,5-Dithiadiazolylum Salts and Related Free Radicals	236
A. Preparation of Mixed 1,3,2,4-/1,2,3,5-Dithiadiazolylum Salts	236
1. From Multi-1,3,2,4-dithiadiazolyl Radicals	236
2. By Sequential Heterocyclic Ring Synthesis	236
B. Physical and Chemical Properties	237
C. X-Ray Diffraction Studies of Mixed 1,3,2,4-/1,2,3,5-Dithiadiazolylum Salts	237
D. Chemistry of 1,3,2,4-Dithiadiazolylum-1,2,3,5-dithiadiazolyl Radicals	238
1. Preparation	238
2. Electron Spin Resonance Spectra	239
3. Magnetism	239
E. Chemistry of 1,2,3,5-/1,3,2,4-Multidithiadiazolyl Radicals	239
1. Preparation	239
2. Electronic Properties	240
XXV. Conclusions	240
References	240

Foreword

Although there have been several brief review articles on dithiadiazolylum chemistry (92CBR148, 92MI1, 92MI2), this is the first comprehensive overview. The steadily increasing number of papers published on this topic in recent years and the possibility of several types of applications have made a more systematic study desirable. In this review article, we aim to describe the major achievements and progress made in this area, from its first beginnings in 1977—a period of just 17 years.

The following abbreviations have been used in this review:

a_E	hyperfine coupling constant to the element E (anisotropic data also have the subscript x , y , z , etc.)
AM1	Austin model 1
c.v.	cyclic voltammetry, cyclic voltammogram
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dsc	differential scanning calorimetry
DMSO	dimethyl sulfoxide
HOMO	highest occupied molecular orbital
g	g -tensor in esr spectra (anisotropic data also have the sub-

	script x, y, z , etc.); g may also be referred to as g_{iso} for isotropic spectra
INDO	intermediate neglect of differential overlap
LUMO	lowest unoccupied molecular orbital
mnt	maleonitriledithiolate (<i>cis</i> -1,2-dicyano-1,2-ethylenedithiolate)
MNDO	modified neglect of diatomic overlap
MO	molecular orbital
mT	milli-Tesla
R	alkyl or aryl substituent
SCE	standard calomel electrode
TBA	tetrabutylammonium
THF	tetrahydrofuran

LIST OF COMPOUNDS

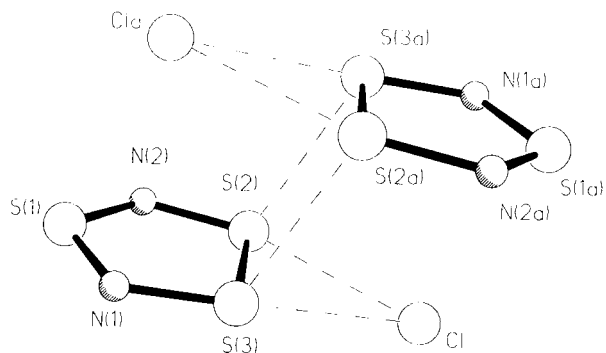
Numbered compounds, referred to in the text, are as follows:

- | | |
|---|---|
| 1. S_3N_2^{+} | 23. $\text{RCS}_2\text{N}_3\text{Cl}_2$ |
| 2. RCNSSN | 24. $[\text{RCS}_3\text{N}_3][\text{S}_3\text{N}_3\text{O}_4]$ |
| 3. RCNSNS | 25. $\text{S}_4\text{N}_4\text{O}_2$ |
| 4. RCSNNS | 26. $\text{S}_3\text{N}_2\text{Cl}_2$ |
| 5. RCNNSS | 27. $\text{RC}(\text{NH})\text{NH}_2$ |
| 6. RCC(R)SSN | 28. $\text{RCS}_2\text{N}_4\text{CR}'$ |
| 7. RCC(R)SNS | 29. $\text{RCN}_2(\text{SiMe}_3)_3$ |
| 8. RCNSSS | 30. <i>sym</i> -Triazine |
| 9. RCC(R)SSS | 31. $[\text{RCNSeSeN}]\text{Cl}$ |
| 10. SSSN | 32. Bicycle: $\text{RCS}_2\text{N}_3/\text{NSN}$, i.e., |
| 11a. $(\text{NSCl})_3$ | RCNSNSN |
| 11b. NSCl | $\begin{array}{c} \quad \\ \text{NSN} \end{array}$ |
| 12. $(\text{NSOR})_3$ | 33. RCNP(R')NSiMe_3 |
| 13. $[\text{S}_3\text{N}_3\text{Cl}_2]\text{X}$ | 34. $\text{RCN}(\text{SiMe}_3)\text{M}(\text{Cl})\text{NSiMe}_3$ |
| 14. S_4N_4 | 35. $\text{RCNE(Cl)NP(R)}_2\text{N}$ |
| 15. $[\text{S}_5\text{N}_5]^+$ | 36. $\text{RCH}=\text{N}-\text{N}=\text{CHR}$ |
| 16. $[\text{N}(\text{SCl})_2]^+$ | 37. $\text{NC.N}=\text{SF}_2$ |
| 17. $[\text{SNS}]^+$ 17a. $[\text{SNS}][\text{AsF}_6]$ | 38. $\text{Me}_3\text{Si.NCN.SiMe}_3$ |
| 18. ArSNSNSAr | 39. $\text{F}_2\text{S}=\text{N.CF}_2.\text{N}=\text{SF}_2$ |
| 19. $[\text{ArSNSNSNSAr}]\text{Cl}$ | 40. Dithiolium cation, |
| 20. Norbornadiene | $[\text{Ph}\overline{\text{CC}}(\text{H})\text{SSC}(\text{H})]^+$ |
| 21. Norbornadiene/ NSCl -adduct (see Scheme 3) | 41. $[(\text{Ph}\overline{\text{CNSSN}})_2\text{Cl}]$ |
| 22. RCN | |

- | | |
|---|--|
| 42. RCS_2N_3 | 67. ClSC(O)Cl |
| 43. Triphenylverdazyl | 68. Ar.C(O)NCS |
| 44. AsF_5 | 69. $\text{Ar.C(O)N}=\text{C(Cl)SCI}$ |
| 45. $[\text{S}_4][\text{AsF}_6]_2$ | 70. $\text{Ar.C(O)N}.\overline{\text{CNSNS}}$ |
| 46. $[\text{SN}][\text{AsF}_6]$ | 71. $\text{Me}_2\text{SnS}_2\text{N}_2$ |
| 47. $\text{R}_2\text{C}=\text{CR}_2$ | 72. COF_2 |
| 48. $\text{RC}\equiv\text{P}$ | 73. $\text{K}[\text{C}(\text{CN})_3]$ |
| 49. RCPSNS | 74. $(\text{NC})_2\text{C}.\overline{\text{CNSNS}}$ |
| 50. $[\text{N}(\text{SBr})_2][\text{AsF}_6]$ | 75. $\text{Zn}[\text{AsF}_6]_2$ |
| 51. $[\text{N}(\text{SF}_2)_2][\text{AsF}_6]$ | 76. FSO_2OMe |
| 52. $[(\text{S}_3\text{N}_2)_2\text{N}][\text{AsF}_6]$ | 77. $[\text{MeOSO}][\text{AsF}_6]$ |
| 53. $[\text{S}_3\text{N}_2\text{Cl}][\text{AsF}_6]$ | 78. $p\text{-C}_6\text{H}_4(\overline{\text{CNSSN}})_2$ |
| 54. PhHgCN | 79. $m\text{-C}_6\text{H}_4(\overline{\text{CNSSN}})_2$ |
| 55. $\text{Hg}(\text{CN})_2$ | 80. $2,5\text{-C}_4\text{H}_2\text{O}(\overline{\text{CNSSN}})_2$ |
| 56. $[\text{Hg}(\overline{\text{CNSNS}})_2][\text{AsF}_6]_2$ | 81. $\text{sym-C}_6\text{H}_3(\overline{\text{CNSSN}})_3$ |
| 57. $[\text{H}\overline{\text{CNSN}}\overline{\text{SCCN}}][\text{AsF}_6]$ | 82. $\text{C}_3\text{N}_3(\text{CN})_3$ |
| 58. $[\text{H}\overline{\text{CNSN}}\overline{\text{SC}}.\overline{\text{CNSNS}}][\text{AsF}_6]_2$ | 83. $\text{C}_3\text{N}_3(\overline{\text{CNSN}})_3$ |
| 59. NSCl_3 | 84. $(\overline{\text{CNSNS}})_2$ |
| 60. $\text{Ph}\overline{\text{CNSC}}(\text{Ph})\text{N}$ | 85. $\text{C}(\overline{\text{CNSNS}})_3$ |
| 61. $\text{NC}.\overline{\text{CC}}(\text{H})\text{SN}\overline{\text{C}}\text{H}$ | 86. $\text{sym-C}_6\text{H}_3(\overline{\text{CNSNS}})_3$ |
| 62. $[\text{BrS}.\overline{\text{CNSNS}}]\text{Br}_3$ | 87. $p\text{-C}_6\text{H}_4(\overline{\text{CNSNS}})_2$ |
| 63. $\text{C}_4\text{H}_8\text{O}$ | 88. $\text{Hg}(\overline{\text{CNSNS}})_2$ |
| 64. $[\text{C}_6\text{H}_5.\overline{\text{CN}}(\text{H})\text{S}(\text{O})\text{N}(\text{H})\text{O}][\text{AsF}_6]$ | 89. $4,4'\text{-Biphenyl}-(\overline{\text{CNSNS}})_2$ |
| 65. $\text{O}\overline{\text{CNSNS}}$ | 90. $m\text{-C}_6\text{H}_4(\overline{\text{CNSNS}})_2$ |
| 66. $\text{Me}_3\text{Si}.\text{NSN}.\text{SiMe}_3$ | 91. $[\overline{\text{SNSN}}\overline{\text{C}}.\overline{\text{CNSN}}]$ |
| | 92. $p\text{-}[\overline{\text{SNSN}}\overline{\text{C}}.\text{C}_6\text{H}_4.\overline{\text{CNSN}}]$ |

I. Introduction: Dithiadiazolyls, New Members of an Old Class of Free Radicals

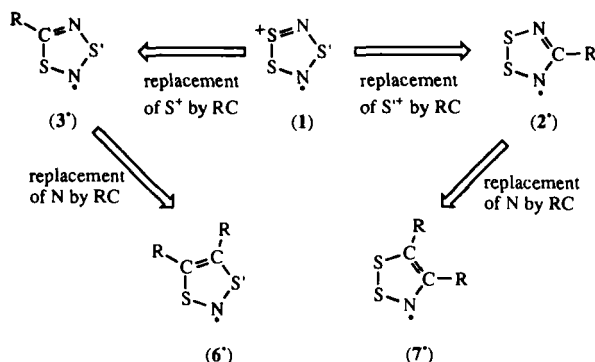
Dithiadiazolyls belong to a class of heterocyclic sulfur–nitrogen free radicals, the first of which, $[\text{S}_3\text{N}_2^{+}]\text{Cl}^{-}$, was prepared as long ago as 1880 (1880CR854). However, it was not until 1974 that the structure of the first S_3N_2^{+} salt was elucidated (74INCL647). The X-ray analysis of many other S_3N_2^{+} salts has since been carried out [75CJC3147; 80CB226; 80ZN(B)1166; 81IC3784; 81ZN(B)293; 84JCS(D)1377; 92JCS(D)3097], and all show oligomeric structures in which two S_3N_2^{+} units are bonded together through overlap of singly occupied molecular orbitals (SOMOs) at sulfur, i.e., through a 4-center, 2-electron, $\text{S} \cdots \text{S}$ interaction. The dimer is linked by weaker secondary interactions to the anion (as illustrated in Fig. 1) and also to other S_3N_2^{+} dimer pairs.

FIG. 1. Structure of $[S_6N_4]Cl_2$.

The parallel $S_3N_2^{+}$ rings in all $S_6N_4^{2+}$ salts take up a trans arrangement with the two rings slightly pulled away from each other. This conformation presumably arises through maximization of cation–anion interactions with minimization of (i) cation–cation repulsions and (ii) repulsive interference between π clouds. The heat of dimerization ($\Delta H_{\text{dim}} = -47 \pm 3$ kJ/mol for $[S_3N_2]Cl$) [86JCS(D)1465] is so low that free-radical monomers can be observed by esr both in the solid state and in solution [86JCS(D)1465; 90MRC189].

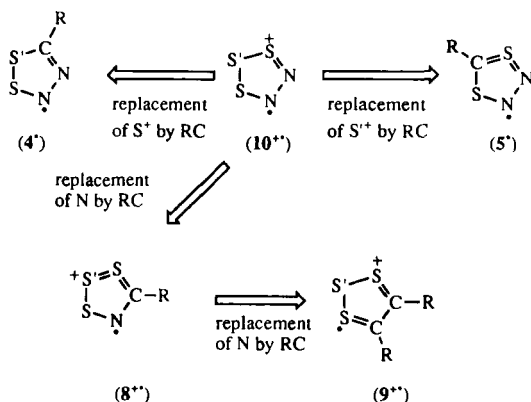
By substituting S^+ with $R-C$ in the $S_3N_2^{+}$ ring (1) (Scheme 1) or in its isomeric counterpart (Scheme 2), isoelectronic ring systems are obtained whose properties can be modified by variation of the substituent R . The $RCN_2S_2^+$ heterocycles, known as dithiadiazolyls (or dithiadiazoles—especially if spin-paired¹), can exist in four possible isomeric forms (2'–5'), of which only the 1,2,3,5-isomer (2') and the 1,3,2,4-isomer (3') have been prepared to date. Molecular orbital calculations (93UP1) on the parent cations (2⁺–5⁺) indicate that the other two isomers could also be formed, although the possible loss of dinitrogen in both these species may be an important factor affecting their stability.

¹ The *neutral*, five-membered CN_2S_2 rings may be either spin-paired (e.g., $PhC(O)NCNSNS$) or free radicals (e.g., $p\text{-NC}_6\text{F}_4\cdot\overline{CNSSN}$). In the latter case the name most commonly now adopted by both US and UK journals is dithiadiazolyl. However, most dithiadiazolyls [especially those of the type $(RCNSSN)$] are spin-paired in the solid state, so they are essentially diamagnetic (see Section IX.D). Consequently, the major component present in the solid state, and sometimes in solution, can legitimately be described as a dithiadiazole or dithiadiazole dimer (this usage is more common in the older literature). Neither naming system is entirely satisfactory, but in accordance with the commonest usage all neutral RCN_2S_2 compounds will be referred to as dithiadiazolyls and their respective cations are described as dithiadiazolylum rather than dithiadiazolium species.

SCHEME 1. Isoelectronic organic radicals based on $\overline{\text{S}}\overline{\text{N}}\text{SSN}^{\cdot+}$.

These MO calculations (Fig. 2) indicate that 2^+ is the more thermodynamically stable of the known isomers, and we shall see later (Sections XXI.A.1 and XXIII.G.2,3) that for the radicals isomerization from 3^{\cdot} to 2^{\cdot} occurs in solution and also in the solid state.

Further substitution of heteroatoms in this manner leads to other members of this class of heterocyclic free radicals, such as the dithiazoles (6^{\cdot} and 7^{\cdot}). Such radicals are outside the scope of this review, but information can be found in the following sources: 84CC573; 84CCC684; 85JCS(D)1405; 87CC66; 91IC3342. Recently, Passmore and co-workers prepared two isoelectronic analogues ($8^{+\cdot}$ and $9^{+\cdot}$) of the isomeric class of cyclic free radicals $\overline{\text{S}}\overline{\text{S}}\text{SN}^{\cdot+}$ ($10^{+\cdot}$, Scheme 2) by the reaction of nitriles

SCHEME 2. Isoelectronic organic radicals based on $\overline{\text{S}}\overline{\text{S}}\text{SN}^{\cdot+}$.

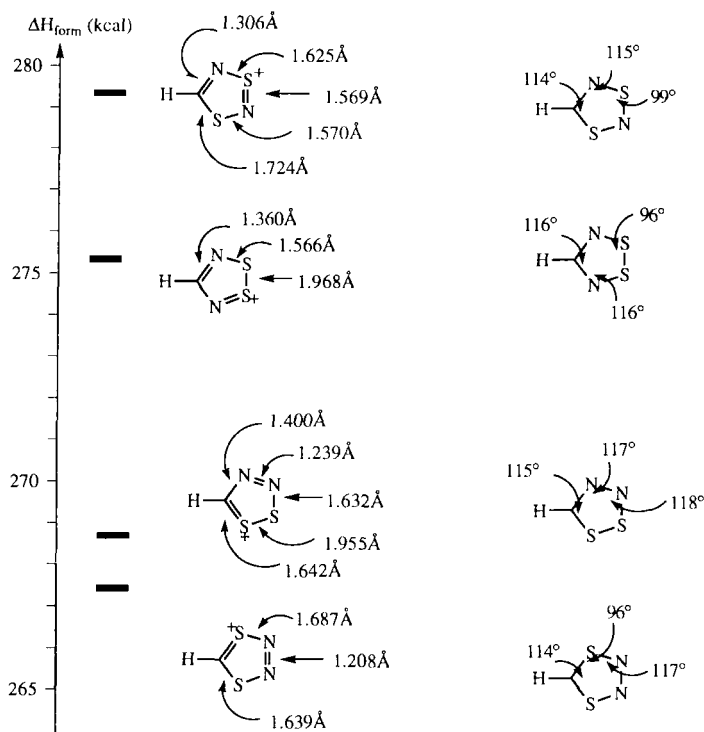


FIG. 2. Stability of different RCN_2S_2 isomers based on MNDO calculations.

or alkynes with a mixture of $\text{S}_8[\text{AsF}_6]_2$ and $\text{S}_4[\text{AsF}_6]_2$ [92IC2274; 92JCS(D)1563].

Much of the early work on dithiadiazolyls (2^\cdot and 3^\cdot) and their cationic dithiadiazolylum counterparts (2^+ and 3^+) involved their synthesis; this work will be discussed in more detail later. The recent development of high-yield routes to these materials from simple precursors has facilitated more extensive studies of their physical properties, particularly in the development and design of organic metals. For instance, polymeric arrays of other neutral radicals such as dithiadiazolyls may provide conducting materials. In comparison, the isolation of organic radicals in the solid state, has led to materials exhibiting spontaneous bulk magnetic response, e.g., ferromagnetism [93N(L)(363)147]. The physical properties of such materials are particularly dependent on the solid-state packing, and consequently a minor modification of the molecular architecture (92MI2) can have major effects on the electronic response. The development of dithiadiazolyl (and isoelectronic diselenadiazolyl, $\text{RCN}_2\text{Se}_2^\cdot$) radicals as organic

metals is discussed more fully later (Sections IX.C and D). A quite different application is the use of dithiadiazolyl radicals as organically soluble metals for coupling reactions (Section XI.A); they also form unusual metal complexes (Section XI.C). The parent dithiadiazolylum cations form unusual charge-transfer salts (Sections V.C and D, and XI.A), and 3^+ salts act as cationic initiators in polymerization reactions (Section XVI.A).

Although the chemistry of such materials is extensive and still expanding rapidly, we hope this review is sufficiently broad to provide a systematic background for the reactions, properties, and potential applications of these materials.

II. Synthetic Approaches to the 1,2,3,5-Dithiadiazolylum Cation

A. THIAZYL CHLORIDE AS A BUILDING BLOCK IN SULFUR-NITROGEN CHEMISTRY

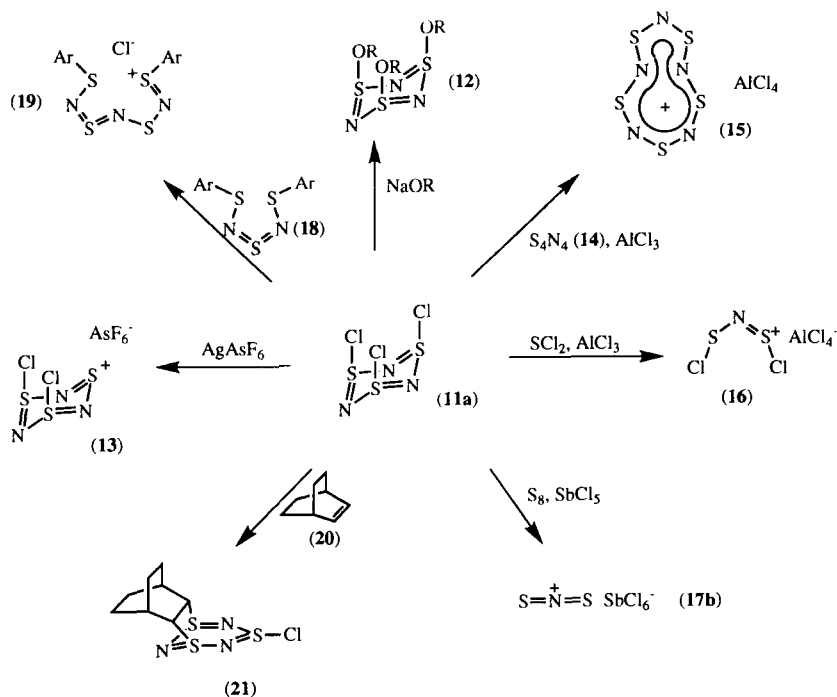
Dithiadiazolylum cations (as the chloride salt) were first prepared in 1977 (77INCL143) from the reaction of thiazyl chloride **11** with organic nitriles. Thiazyl chloride **11** exists as a trimer **11a** in the solid state (61AX562), but partial dissociation to the monomer **11b** occurs in the vapor phase (70IC1079) and in solution (88IC2749).



The trimer has been used as a convenient source of SN units in a wide variety of reactions (79PS421; 85CRV341; 85MI1). A comprehensive examination of the chemistry of this reagent is beyond the scope of this review, but the high-yielding reaction chemistry may be highlighted by a few examples, as illustrated in Scheme 3 and outlined below.

1. Ring-Retention Reactions of $(\text{NSCl})_3$

Reaction of **11** with alkoxides (87IM2161) or epoxides (79JINC1421) leads to formation of $(\text{NSOR})_3$ **12**, in which the structure of the six-membered ring is retained. Reaction with Lewis acids, and presumably suitable silver salts, can lead to the formation of salts $[\text{S}_3\text{N}_3\text{Cl}_2]\text{X}$ **13**, although breakdown to other S/N cations is also known (85MI1).

SCHEME 3. Reactivity of $(\text{NSCl})_3$

2. Use of $(\text{NSCl})_3$ in Ring-Expansion Reactions

Reaction of the sulfur–nitrogen cage, S_4N_4 **14**, with thiazyl chloride **11** in the presence of a chloride acceptor leads to the formation of salts of the 14- π aromatic cation, S_5N_5^+ (77IS188), **15**.

3. Use of $(\text{NSCl})_3$ in Chain Formation

Thiazyl chloride **11** reacts with SCl_2 or S_8 in liquid SO_2 at room temperature in the presence of a Lewis acid (or silver salt) to form salts of $[\text{N}(\text{SCl})_2]^+$ **16** and $[\text{SNS}]^+$ **17**, respectively, typically in excess of 80% recovered yield [79INCL175; 87JCS(D)1565; 92JCS(D)3097], whereas reaction of **11** with DMSO in CH_2Cl_2 yields $[\text{Me}_2\text{SNSMe}_2]\text{Cl}$ (82AG(E)538). Salts of **17** possess an extensive cycloaddition chemistry which is described in more detail in Section XII.A, while the reaction chemistry of **16** is currently being developed [90CJC852; 90JCS(D)1517; 92JCS(D)3097]. The chemistry of $[\text{Me}_2\text{SNSMe}_2]^+$ has yet to be studied.

4. (NSCl)₃ in Chain Expansion

In liquid SO₂ or CH₂Cl₂ solution **11** inserts an SN unit into the sulfur–nitrogen chain, Ar₂S₃N₂ **18**, to give the salt [Ar₂S₄N₃]Cl **19** in >75% yield (93UPI). To date, no further studies have been carried out to determine whether this chain-extension reaction is more general.

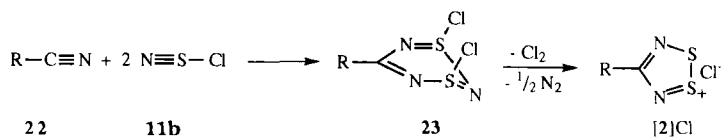
5. (NSCl)₃ in Heterocyclic-Ring Formation

Thiazyl chloride **11** reacts with norbornadiene **20** and other unsaturated centers to form heterocyclic rings (see Scheme 3). Such reactions are frequently complex; e.g., **11** + **20** proceeds via a dechlorination/cycloaddition process to form **21** (91IC1392), whereas reaction with organic nitriles leads ultimately to formation of 1,2,3,5-dithiadiazolylium salts [2]Cl.

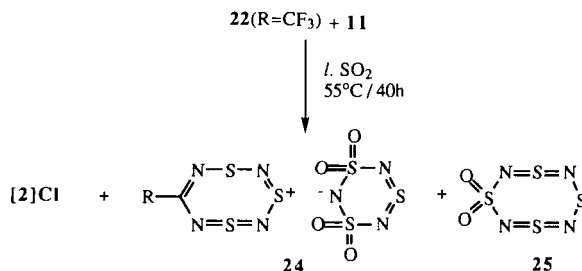
B. REACTION OF NITRILES WITH (NSCl)₃

When an organic nitrile RCN (**22**) is refluxed in the presence of **11**, a cyclization reaction occurs, forming [2]Cl in up to 50% recovered yield depending on the functionality R [77INCL143; 79JCS(P1)1192; 84AG(E)988; 85CB3781]. The yield of [2]Cl is particularly dependent on reaction conditions [84AG(E)988] with best results being achieved after extended periods of heating. The sulfur required to balance the equation can be considered to arise from the thermal decomposition of **11**, although the reaction is, in fact, more complex (see below). At lower temperatures (≤65°C), variable quantities (up to 90%) of a dithiatriazine **23** have been isolated, formed by cyclization of two equivalents of **11b** with RCN [84AG(E)988; 86IC47]. Similar high yields of **23** were obtained by carrying out reactions at room temperature under UV irradiation (89CC96). Subsequent thermal decomposition of **23** with the loss of nitrogen and chlorine leads to [2]Cl (see below). Consequently, the highest yields of [2]Cl are achieved after extended periods of reflux. The ring contraction from **23** to [2]Cl may also be achieved under milder conditions via sodium azide reduction (86IC47).

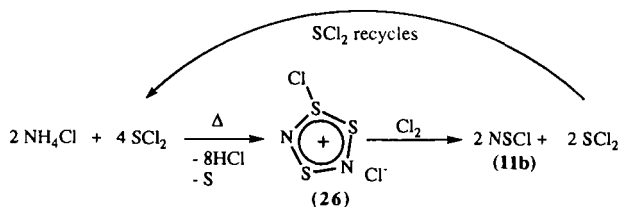
Although the formation of [2]Cl would appear simple, a variety of other



side products have also been isolated under specific conditions. For example, reaction of CF_3CN with **11** in liquid SO_2 [84AG(E)988; 85CB3781] gave the desired product [**2**] Cl (30%, $\text{R} = \text{CF}_3$) and also a salt **24** of the eight-membered cyclic cation, RCNSNSNSN^+ (4%) and the neutral $\text{S}_4\text{N}_4\text{O}_2$ ring **25**.



While examining the chemistry of **11** with metal halides in acetonitrile, Dehnicke *et al.* found that $[2]_5[\text{CoCl}_4]\text{Cl}_3$ could also be isolated [86ZAC(536)153]. Because of the large quantities of **11** required for the poorer-yielding preparations of dithiadiazolylium chlorides, $[2]\text{Cl}$, other bulk-scale (5–50 g) approaches to these salts were examined. Of particular importance was the discovery [79JCS(P1)1192; 83JCS(P1)1181] that $[2]\text{Cl}$ could be prepared from cheap, commercially available starting materials: a refluxing mixture of parent nitrile and sulfur dichloride containing ammonium chloride under an atmosphere of chlorine could provide moderate yields (10–30%) of $[2]\text{Cl}$. The mixture of NH_4Cl and SCl_2 acts as an in situ source of thiazyl chloride **11** (see Scheme 4), and the compound $[\text{S}_3\text{N}_2\text{Cl}]\text{Cl}$ **26** also tends to be formed as a by-product. However, the latter compound reacts with chlorine (67IS102) to form more **11**, and so its formation is suppressed by the chlorine atmosphere. Salt $[2]\text{Cl}$ can be separated from the reaction mixture by first washing with diethyl ether (to remove unreacted SCl_2 and parent nitrile), followed by Soxhlet extraction with liquid SO_2 .



SCHEME 4. *In situ* preparation of $(\text{NSCl})_3$ from $\text{NH}_4\text{Cl}/\text{SCl}_2$ via $\text{S}_3\text{N}_2\text{Cl}_2$.

This type of condensation reaction between N—H and S—Cl bonds led workers to examine the reactivity of amidines with SCl_2 .

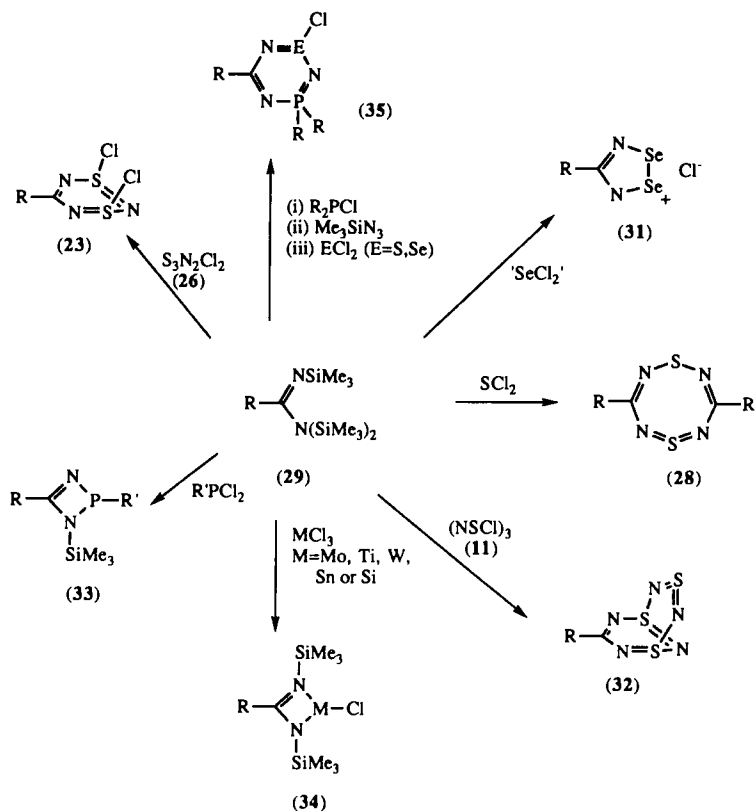
C. REACTION OF AMIDINES AND AMIDINIUM SALTS WITH SCl_2

The first reaction of amidines $\text{RC}(\text{NH})\text{NH}_2$ **27** with SCl_2 to yield $[\text{2}]\text{Cl}$ involved benzamidine hydrochloride [79JCS(P1)1192]. Subsequently, other workers reported the preparation of $[\text{2}]\text{Cl}$ ($\text{R} = \text{Me}_2\text{N}-$, *m*- and *p*- NC_6H_4- , furenyl and thienyl derivatives) from similar condensation reactions [89CC1137; 89JA6147; 89JCS(P1)2495; 92IC1802]. In many cases, yields were moderate but could be improved by using the free amidine (rather than the amidinium salt) or by the addition of a base (e.g., DBU) to abstract the HCl formed (81JA1540; 89CC1137).

When condensation reactions are carried out at low temperature with a deficit of SCl_2 , dithiatetrazocines **28** may also be formed, usually in low yield [89CC1137; 89JCS(P1)2495]; see Scheme 5. However, under carefully controlled conditions, using silylated amidines **29** or their N-lithio salts, Roesky *et al.* isolated a series of derivatives of **28** in good yield (50–60%) (89CB1067). [By carrying out such condensation reactions in the presence of two amidines, mixed derivatives of **28** (where $\text{R} \neq \text{R}'$) can also be formed in low yield (89JCS(P1)2495). For aryl-substituted derivatives of **28**, the eight-membered ring is planar 10π -aromatic, but for R_2N -substituted systems the ring becomes folded (81JA1540)]. Reaction of **28** with AgAsF_6 (89CB1067) leads to breakdown of the eight-membered C/N/S ring to form a mixture of dithiadiazolylum salts, $[\text{2}][\text{AsF}_6]$ and $[\text{2}]_3[\text{AsF}_6]_2\text{Cl}$.

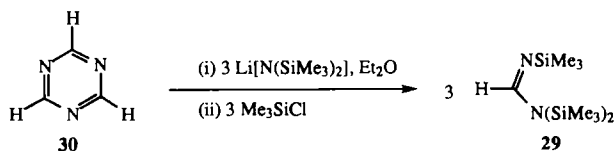
The recovered yield of $[\text{2}]\text{Cl}$ can be maximized (typically >70%) by slow addition of the amidine or its N-lithio salt to excess SCl_2 , followed by warming to a low reflux for ~ 1 h in an inert solvent such as MeCN, CCl_4 , or CH_2Cl_2 . This route has been used extensively in recent years for preparing aryl derivatives of $[\text{2}]\text{Cl}$ and is the most convenient route to many of these salts [89JA9276; 89JCS(P1)2495; 91JA582; 91JA3559; 92CJC919; 92JA5000; 92JCS(D)1449; 93JCS(D)967; 93JCS(D)1421]. Purification can be achieved readily by washing with MeCN, CH_2Cl_2 , or CCl_4 to remove unreacted SCl_2 and Me_3SiCl by-product, followed by drying in vacuo. In cases where the N-lithio salt has been used, separation of soluble $[\text{2}]\text{Cl}$ from LiCl can be achieved by Soxhlet extraction with liquid SO_2 . The $[\text{2}]\text{Cl}$ presumably extracts as the chlorosulfite, $[\text{2}][\text{SO}_2\text{Cl}]$.

Many persilylated amidines are readily prepared by the reaction of the parent nitrile with $\text{Li}[\text{N}(\text{SiMe}_3)_2]$ in Et_2O , followed by addition of Me_3SiCl to the N-lithio salt (87JOM161) as outlined in Scheme 5. This methodology



SCHEME 5. Preparation of silylated amidines from nitriles and subsequent reaction with $(\text{NSCl})_3$, SCl_2 , $\text{S}_3\text{N}_2\text{Cl}_2$, etc.

is susceptible to side reactions when there are protons α to the cyano group, and consequently there are limitations for the preparation of some alkyl derivatives. However Oakley *et al.* have recently found that *sym*-triazine **30** reacts with $\text{Li}[\text{N}(\text{SiMe}_3)_2]/\text{Me}_3\text{SiCl}$ in Et_2O to form the parent silylated amidine $\text{HC}(\text{=NSiMe}_3)\text{N}(\text{SiMe}_3)_2$ (**29**, with $\text{R} = \text{H}$) (92CC1265). Similar reactions with other *sym*-triazines may facilitate the synthesis of related alkylated amidines, although the general applicability of this route has yet to be established.



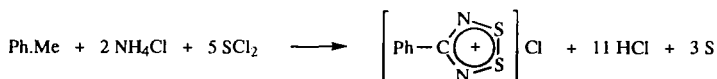
Condensation of silylated amidines with "SeCl₂" (i.e., an in situ 1:1 mixture of SeCl₄ and Se or SeCl₄ and Ph₃Sb) has also allowed the synthesis of the isostructural diselenadiazolium salts, [RCNSeSeN]Cl **31** (89JA9276; 91JA582; 91JA3559; 92CC1265; 92IC1802; 92JA1729; 92JA5000). In comparison, condensation reactions between amidines and sulfur–nitrogen halides such as **26** and **11**, lead to **23** and the bicyclic systems **32**, respectively (Scheme 5) [83ZN(B)347; 85CC929; 85JA7710; 86AX(C)900; 89JA1579]. Silylated amidines have recently been used as building blocks in the synthesis of a variety of other heterocyclic systems. For example condensation reactions of **29** have led to the formation of compounds based on the CN₂P (**33**), CN₂[M] (**34**, M = Mo, Ti, W, Sn, Si), and CN₃EP (**35**, E = S, Se) rings (88CB1403; 88CB1681; 89IC3931; 90JA2249; 92IC442).

A remarkable number of alternative routes to [2]Cl exist, the majority of which are more specific than those outlined in Sections II.B and C above, and these are described below.

D. OTHER ROUTES TO THE 1,2,3,5-DITHIADIAZOLYLUM RING SYSTEM

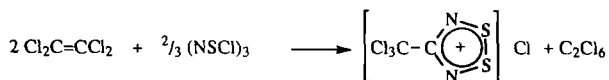
1. From Toluene, NH₄Cl, and SCl₂

Curiously, when NH₄Cl and SCl₂ are heated in refluxing toluene, a small amount (3%) of [2]Cl (R = Ph) is formed [83JCS(P1)1181]. Intermediates in this sequence of reactions have not been isolated, although the reaction must proceed through deprotonation of the methyl group, presumably through a condensation reaction with SCl₂.



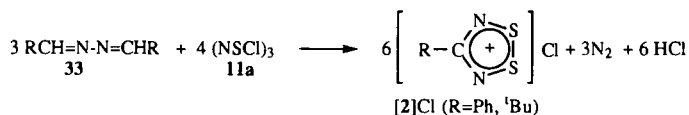
2. From Tetrachloroethylene and (NSCl)₃

Cycloaddition of **11** with tetrachloroethylene produced [2]Cl (R = CCl₃) in 13% yield [79JCS(P1)1192]. The mechanism of this reaction has not been established, but must involve the activation of C—Cl bonds.



3. From Aldazines and (NSCl)₃

Roesky *et al.* have shown that reaction of **11** with several aldazines RC(H)=N—N—C(H)R **36** provides a convenient route to **[2]Cl** ($\text{R} = \text{Ph}$, 92%; $\text{R} = t\text{Bu}$, 28%), although the yield would appear to be particularly dependent on the nature of the substituent R (78CB2960).

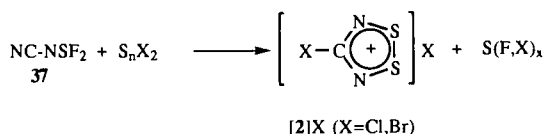


4. From Trichloroacetic Anhydride and (NSCl)₃

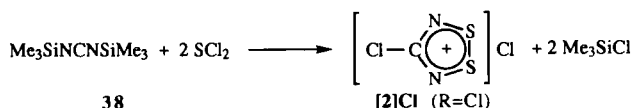
Reaction of trichloro-acetic anhydride with **11** led to the isolation of **[2]Cl** ($\text{R} = \text{CCl}_3$) in unspecified yield [88ZAC(562)31].

5. Preparation of $[\text{X}\overline{\text{C}}\text{NSSN}]^+$ Salts ($\text{X} = \text{F}, \text{Cl}, \text{Br}$)

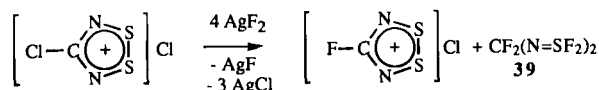
The halo-substituted **[2]⁺** salts ($\text{R} = \text{Cl}, \text{Br}$) were initially prepared in 1983 by Mews and co-workers (83CB416) from NC.N=SF_2 **37** and the sulfur halide SCl_2 or S_2Br_2 .



However, the chloro derivative **[2]Cl** ($\text{R} = \text{Cl}$) can be more conveniently prepared from the readily accessible bis(trimethylsilyl) carbodiimide **38** by condensation with SCl_2 at 50°C (83CB416). The instability of SF_2 has prevented analogous formation of $\text{FCN}\overline{\text{C}}\text{N}\text{SSN}^+$.



Consequently an alternative approach was required. Halogen exchange of **[2]Cl** ($\text{R} = \text{Cl}$) with AgF_2 in chloroform at -60°C (85CB3781) provided such a method, although the salt was isolated only in 25% recovered yield; the desired product was contaminated with the perfluorinated compound **39**. The problems associated with the preparation and isolation of **[2]F** via fluorination reactions are also discussed in Section XI.A.



E. CONCLUSIONS

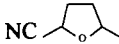


Many aryl-substituted dithiadiazolylium salts are most conveniently prepared in good yield (frequently 70+%) from the condensation reaction of SCl_2 with amidines, silylated amidines, or their salts. However the synthesis of alkyl-substituted salts generally requires more specific conditions. In some circumstances, reaction of the parent nitrile with NH_4Cl and SCl_2 provides the required salt in moderate yield (up to 30%). For more sensitive substituents, which may undergo side reactions with SCl_2 at elevated temperatures, milder approaches can be employed, such as UV irradiation of the parent nitrile/ $(\text{NSCl})_3$ mixture at room temperature, followed by thermal or chemical degradation of the intermediate six-membered heterocycle. The simplest halo-substituted salts $[\text{X}.\dot{\text{C}}\text{NSSN}]\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{etc.}$) are prepared by specific routes. The syntheses of all currently reported salts $[\text{2}]\text{X}$ are outlined in Table I (the preparation of multifunctional species is described in Section XXII.A).

III. Theoretical Studies of 1,2,3,5-Dithiadiazolylium Heterocycles

Theoretical calculations have been performed by several workers on the RCNSSN^+ cation ($\text{R} = \text{H}, \text{H}_2\text{N}, \text{Cl}$) in order to rationalize the nature of UV/visible spectra [85JST1; 86IC2119; 89JA6147; see also Section IV.B) and to investigate the bonding [90JCS(D)2793]. These calculations have also been used in rationalizing the esr spectra of the corresponding 1,2,3,5-dithiadiazolyl free radicals 2^\cdot [86JCS(D)1465]. Of particular importance are the frontier molecular orbitals (HOMO, SOMO, LUMO), which have been used extensively in describing many physical features of the $2^+/\text{2}^\cdot$ ring systems. The frontier orbitals for 2^+ ($\text{R} = \text{H}$; Fig. 3) are composed of a combination of in-plane σ -bonding and out-of-plane π orbitals. The sizes of the orbitals shown in Figures 3 and 4 are approximately proportional to the orbital coefficients indicated by the MO calculations.

Modification of such orbitals by substituent groups occurs readily, most conspicuously for substituents possessing lone-pairs, e.g., $\text{H}_2\text{N}-$ and $\text{Cl}-$ (85JST1): these lone pairs affect the lowest energy electronic transitions and therefore the colors of these materials in solution (see Section

TABLE I
SYNTHESES OF 1,2,3,5-DITHIADIAZOLYLIUM SALTS^a, RCN⁺SSN⁺ (2⁺)

Substituent	<i>Aromatic</i>		Reference
	Route	Yield ^b (%)	
Ph	PhCH=N—N=CHPh/(NSCl) ₃	92	78CB2960
	[PhC(NSil) ₂] ₂ Li/SCl ₂	77	93JCS(D)967
	PhCN ₂ Si ₂ /SCl ₂	60	89JCS(P1)2495
	PhC=NH(NH ₂).HCl/SCl ₂ /DBU	54	89JCS(P1)2495
	PhCN/(NSCl) ₃	50	79JCS(P1)1192
	PhCN/NH ₄ Cl/SCl ₂	25–30	79JCS(P1)1192
			83JCS(P1)1181
	PhC(=NH)(NH ₂).HCl/SCl ₂	10–19	79JCS(P1)1192
			83JCS(P1)1181
	PhMe/NH ₄ Cl/SCl ₂	3	83JCS(P1)1181
<i>p</i> -Cl.C ₆ H ₄	[<i>p</i> -Cl.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	75	93JCS(D)967
	<i>p</i> -Cl.C ₆ H ₄ .CN/NH ₄ Cl/SCl ₂	15	83JCS(P1)1181
			89JCS(D)1705
<i>p</i> -Br.C ₆ H ₄	[<i>p</i> -Br.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	60	93JCS(D)967
<i>p</i> -Me.C ₆ H ₄	[<i>p</i> -Me.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	55	93JCS(D)967
<i>p</i> -O ₂ N.C ₆ H ₄	[<i>p</i> -O ₂ N.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	65	93JCS(D)967
<i>p</i> -F ₃ C.C ₆ H ₄	[<i>p</i> -F ₃ C.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	58	93JCS(D)967
<i>p</i> -MeO.C ₆ H ₄	[<i>p</i> -MeO.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	67	93JCS(D)967
<i>p</i> -MeS.C ₆ H ₄	[<i>p</i> -MeS.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	60	93JCS(D)967
<i>p</i> -F.C ₆ H ₄	[<i>p</i> -F.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	63	93JCS(D)967
<i>p</i> -NC.C ₆ H ₄	[<i>p</i> -NC.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	72	92JCS(D)1449
			93JCS(D)967
	[<i>p</i> -NC.C ₆ H ₄ .C(=NH)NH ₂]/SCl ₂	—	92IC1802
<i>m</i> -NC.C ₆ H ₄	[<i>m</i> -NC.C ₆ H ₄ .C(NSil) ₂] ₂ Li/SCl ₂	70	93JCS(D)967
	[<i>m</i> -NC.C ₆ H ₄ .C(=NH)(NH ₂) ₂]/SCl ₂	—	92IC1802
C ₆ F ₅	[C ₆ F ₅ .C(NSil) ₂] ₂ Li/SCl ₂	76	93JCS(D)967
	NC.C ₄ H ₂ O.C(=NSil)NSil ₂ /SCl ₂	—	92CJC919
	C ₄ H ₃ O.C(=NH)NH ₂ .HCl/SCl ₂	—	89JCS(P1)2495
	C ₄ H ₃ S.C(=NH)NH ₂ .HCl/SCl ₂	69	89JCS(P1)2495
<i>Aliphatic</i>			
Me	MeCN/NH ₄ Cl/SCl ₂	10	83JCS(D)1181
<i>n</i> -Pr	<i>n</i> PrCN/NH ₄ Cl/SCl ₂	—	89JCS(D)1705
<i>t</i> Bu	<i>t</i> BuCH=N—N=CH <i>t</i> Bu/(NSCl) ₃	28	78CB2960
	<i>t</i> BuCN/(NSCl) ₃	—	77INCL143
	<i>t</i> BuCN ₃ S ₂ Cl ₂ /heat	—	89CC96
CCl ₃	Cl ₃ C.CN ₃ S ₂ Cl ₂ /heat	87	89CC96
	Cl ₃ CCN/(NSCl) ₃	42	79JCS(P1)1192
	Cl ₃ CCN/NH ₄ Cl/SCl ₂	30	79JCS(P1)1192

(Continues)

TABLE I (Continued)

Substituent	<i>Aliphatic</i>		Reference
	Route	Yield ^b (%)	
CF ₃	C ₂ Cl ₄ /(NSCl) ₃	13	79JCS(P1)1192
	(Cl ₃ CCO) ₂ O/(NSCl) ₃	—	88ZAC(562)31
	F ₃ CCN/(NSCl) ₃	30–45	84AG(E)988; 85CB3781
	F ₃ C.CN ₃ S ₂ Cl ₂ /heat	—	84ZN(B)1389
PhCH ₂	PhCH ₂ CN/NH ₄ Cl/SCl ₂	17	89TH1
Me ₂ N	Me ₂ N.CN ₃ S ₂ Cl ₂ /heat	91	89CC96
	Me ₂ N.C(=NH)NH ₂ .HCl/SCl ₂	54	89JA6147
Et ₂ N	Et ₂ N.CN ₃ S ₂ Cl ₂ /heat	74	89CC96
	Et ₂ N.CN ₃ S ₂ Cl ₂ /NaN ₃	22	86IC2119
<i>i</i> Pr ₂ N	<i>i</i> Pr ₂ N.CN ₃ S ₂ Cl ₂ /heat	—	89CC96
Cl	(SiI)NCN(SiI)/SCl ₂ ^a	81	83CB416
	NC.N=SF ₂ /S _x Cl ₂	50	83CB416
Br	NC.N=SF ₂ /S _x Br ₂	56	83CB416
F	ClCNSSNCl/AgF ₂	28	85CB3781

^a SiI = SiMe₃.^b If specified.

IV.B). However, for the majority of alkyl and aryl derivatives, the relative energies are similar to those outlined in Figure 3. Although the charge distribution around the heterocyclic 2⁺ ring is also modified slightly by substituents, the sulfur atoms possess the majority of the positive charge, as anticipated from simple electronegativity arguments (85JST1): e.g., for 2⁺ (R = H), S (+0.5), N (−0.3), C (+0.6). For simple derivatives, atom–atom overlap populations are very similar for CN, NS, and SS bonds and are composed of both σ and π components. There are three occupied π MOs, all of which provide a net bonding contribution, and 2⁺ heterocycles can be considered to be 6 π aromatic (85JST1).

Several comparative studies of molecular structure in 2⁺ and 2[•] rings have been undertaken [89JCS(D)2229; 90JCS(D)2793; 91JCS(D)1105; 92CBR148; 92MI2]; frontier orbitals have proved very helpful in rationalizing differences in both structure (e.g., S—S bond distances) and reactivity.

Some π -donor anions (such as S₃N₃[−]), which interact out-of-plane with the 2⁺ cation, facilitate charge transfer into the π -based unoccupied molecular orbital which is of a₂ symmetry and therefore antibonding with respect to both d_{SS} and d_{SN} (see Fig. 4a). Consequently, salts of this type exhibit longer SS bonds than salts of weakly interacting anions such as AsF₆[−]. Similarly, complete reduction of 2⁺ to 2[•] produces partial occupancy of the same a₂ orbital and thus d_{SS} in (2[•])₂ is greater than in 2⁺ (Fig. 4b). In the extreme, when filled metal orbitals donate electron density into the

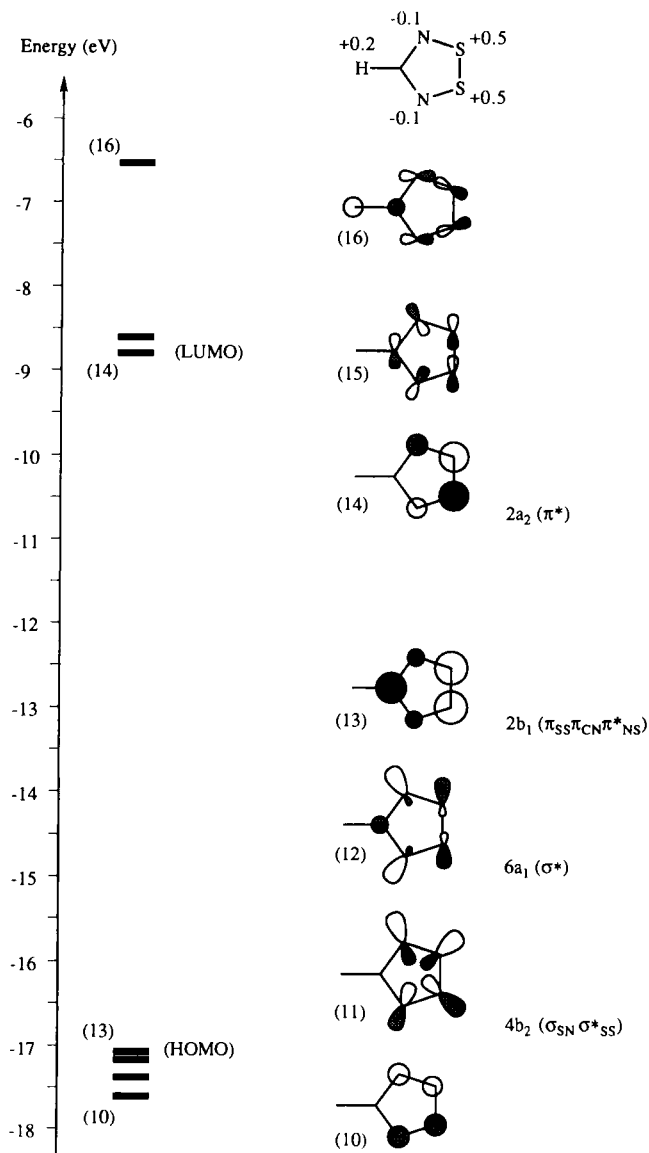


FIG. 3. Frontier molecular orbitals and calculated partial charges for $[\overline{\text{HCNSSN}}]^+$.

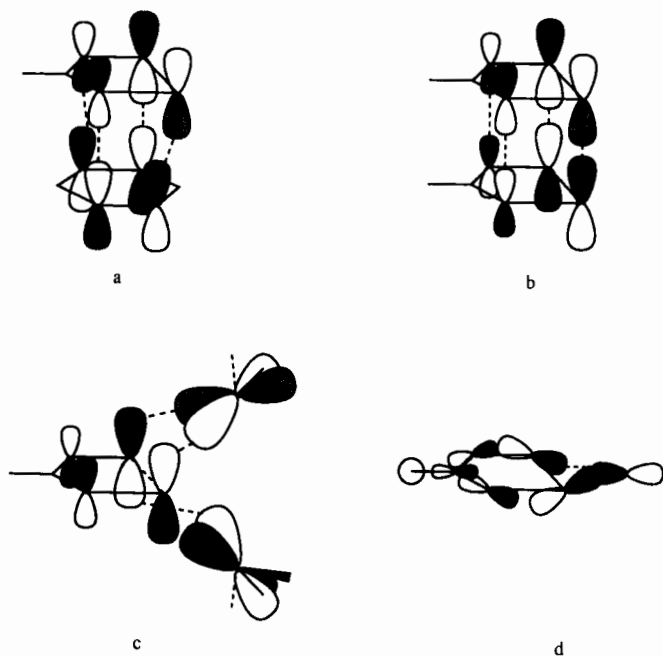


FIG. 4. Orbital interactions diagram for $[\text{Ph.CN}^+\text{SSN}]$ salts: (a) $[\text{Ph.CN}^+\text{SSN}][\text{S}_3\text{N}_3]$; (b) $[\text{Ph.CN}^+\text{SSN}]_2$; (c) $\text{Cp}_2\text{Ni}_2[\text{Ph.CN}^+\text{SSN}]$; (d) $[\text{Ph.CN}^+\text{SSN}]\text{Cl}$.

heterocyclic ring, e.g., in the metal complex $\text{Cp}_2\text{Ni}_2[\text{Ph.CN}^+\text{SSN}]$ [91JCS(D)1105; see also Section XI.C], the increase in metal-sulfur bonding is accompanied by a larger increase in d_{SS} and, to a lesser extent d_{SN} (Fig. 4c). Some small anions, such as Cl^- , interact with the $\text{S}^{\delta+}$ atoms through an in-plane interaction. This interaction can be considered to arise through interaction of the Cl^- lone-pair orbitals with the b_1 unoccupied orbital of 2^+ , leading to a net 3-center, 2-electron bonding interaction, thus strengthening the SS bond (Fig. 4d).

IV. Physical Properties of Mono-1,2,3,5-Dithiadiazolylium Salts

A. MULTINUCLEAR NUCLEAR MAGNETIC RESONANCE SPECTRA

Until recently, the dithiadiazolylium rings have not been conveniently studied by nmr because of the low natural abundance of $\text{S} = 1/2$ isotopes [^{33}S 0.76%, ^{15}N 0.37%, and ^{13}C 1.1% (80MI1)] and the poor resolution often associated with ^{14}N nmr. However, with improvements in nmr technology, a few data have become available (Table II). Nuclear magnetic resonances for substituent groups generally show a shift to low field (rela-

TABLE II
MULTINUCLEAR NMR DATA FOR 1,2,3,5-DITHIADIAZOLYLIUM SALTS

Compound	$^1\text{H}^a$	$^{19}\text{F}^b$	$^{13}\text{C}^c$	$^{14}\text{N}^d$	Reference
$[\text{CF}_3.\overline{\text{CNSSN}}]\text{Cl}$		-73.58			85CB3781
$[\text{F}.\overline{\text{CNSSN}}][\text{AsF}_6]$		-54.1	+171.3		85CB3781
$[\text{tBu}.\overline{\text{CNSSN}}]\text{Cl}$	+1.67			-135	85CB3781; 89CC96
$[\text{Me}_2\text{N}.\overline{\text{CNSSN}}]\text{Cl}$				-318 (Me_2N)	89CC96
				-133 (CN_2S_2)	
$[\text{Et}_2\text{N}.\overline{\text{CNSSN}}]\text{Cl}$				-296 (Et_2N)	89CC96
				-127 (CN_2S_2)	
$[\text{CCl}_3.\overline{\text{CNSSN}}]\text{Cl}$				-181	89CC96
$[\text{Ph}.\overline{\text{CNSSN}}]\text{X}$	7.6-9 ^e				85CB3781
	8.51-9.5 ^e				

^a With reference to $(\text{CH}_3)_4\text{Si}$.

^b Internal standard CF_3Cl .

^c Internal standard $\text{C}_6\text{D}_6/\text{CF}_3\text{Cl}$.

^d Internal standard MeNO_2 .

^e Depending on the anion X.

tive to the parent nitrile) due to the positive charge associated with the dithiadiazolylium ring. It should perhaps be noted that the similar ^1H nmr data for all $[\text{Ph}\overline{\text{CNSSN}}]^+$ salts, irrespective of the counterion (SbCl_6^- , CF_3SO_3^- , $\text{N}(\text{SO}_2\text{F})_2^-$, BF_4^- , PF_6^- , and Cl^-), are indicative of a high degree of dissociation in solution (78CB2960).

B. UV/VISIBLE SPECTRA

Dithiadiazolylium salts are often brightly colored in the solid state, typically red, orange, or yellow (with the more interacting anions tend to be darker materials: purple, black, or dark green) [83JCS(P1)1181]. Although no studies of the reflectance spectra of these salts have been reported, solution UV/visible spectra of a variety of 1,2,3,5-dithiadiazolylium salts have been described [79JCS(P1)1192; 86IC2119; 89JA6147; 89JCS(P1)2495]. These results are collated in Table III.

The UV/visible transitions, discussed at length by Oakley (89JA6147) and previously by Chivers (86IC2119) and Trsic (85JST1), have been correlated with results of MO calculations on ground-state and excited-state structures. They indicate that for dialkylamino derivatives 2^+ ($\text{R} = \text{R}_2\text{N}-$), an $n_\pi-\pi^*$ transition (between $^1\text{A}_1$ adiabatic and $^1\text{B}_2$ states) gives rise to absorptions at ~ 530 nm. Such absorptions give these derivatives an unusually dark color in solution (86IC2119; 89JA6147) (contrast

TABLE III
 UV/VISIBLE DATA FOR 1,2,3,5-DITHIADIAZOLYLIUM SALTS

Compound	Solvent	λ_{\max} (7) nm		Reference
[Me ₂ N. $\overline{\text{CNSSN}}$]Cl	MeCN	532 (3×10^2)	398 (2×10^2)	86IC2119; 89JA6147
[Et ₂ N. $\overline{\text{CNSSN}}$]Cl	MeCN	520–530		86IC2119
[<i>t</i> Bu. $\overline{\text{CNSSN}}$]Cl	MeCN	454	355 300 250	86IC2119
[Cl ₃ C. $\overline{\text{CNSSN}}$]Cl	MeCN	262	228	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl	MeCN	370	276 222	86IC2119
[Ph. $\overline{\text{CNSSN}}$]Cl	CH ₂ Cl ₂	395 (680)		89JCS(P1)2495
[Ph. $\overline{\text{CNSSN}}$]Cl	CH ₂ Cl ₂	396 (690)		79JCS(P1)1192

the typical pale yellow–orange color of many alkyl and aryl dithiadiazolylium salts in solution). Thus CNSSN-ring absorptions are quite sensitive to the nature of the side group (86IC2119). A second transition for dialkylamino derivatives has been tentatively assigned to a HOMO \rightarrow LUMO+1 excitation (89JA6147).

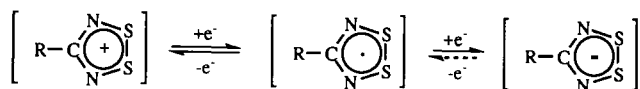
Theoretical work by Trsic *et al.* (85JST1) showed that the substituent may greatly affect the lowest-energy-allowed electronic transition. This is particularly the case for substituents bearing lone pairs or other active chromophores. For example, for the three simple derivatives 2^+ (R = H, Cl, and H₂N), each possesses a different set of low-energy transitions: For 2^+ (R = H) these are $4b_2 \rightarrow 2a_2$ [HOMO \rightarrow LUMO, $\sigma \rightarrow \pi^*$] and $2b_1 \rightarrow 2a_2$ [HOMO-2 \rightarrow LUMO, $\pi \rightarrow \pi^*$]; for 2^+ (R = Cl) these are $5b_2 \rightarrow 2a_2$ [$n_\sigma(\text{Cl}) \rightarrow \pi^*$] and $3b_1 \rightarrow 2a_2$ [$n_\pi(\text{Cl}) \rightarrow \pi^*$]; and for 2^+ (R = H₂N) these are $3b_1 \rightarrow 2a_2$ [$n_\pi(\text{NH}_2) \rightarrow \pi^*$] and $5b_2 \rightarrow 2a_2$ [$\sigma \rightarrow \pi^*$].

Since the color of these salts is modified by substituents containing lone pairs or chromophores, each new derivative requires its own analysis. For substituents that do not possess a potentially UV/visible active chromophore, pale-colored solutions are indicative of an essentially spin-forbidden transition.

The nature of the solvent also modifies the absorption maxima, as exemplified in the case of [Ph $\overline{\text{CNSSN}}$]Cl: λ_{\max} for this material is shifted by ~ 25 nm when using CH₂Cl₂ instead of MeCN [79JCS(P1)1192; 86IC2119; 89JCS(P1)2495]. Such a change in absorption maximum can be attributed to the coordinating nature of the solvent; indeed, several dithiadiazolylium salts have been crystallized as RCN solvates (R = Me, Ph) [90AX(C)140; 93JCS(D)1421], in which the nitrile functionality coordinates weakly to the sulfur atoms of the 2^+ heterocycle via an in-plane interaction with the nitrile nitrogen atom.

C. ELECTROCHEMICAL STUDIES

An extensive study of some 11 para-substituted aryl derivatives, 2^+ ($R = p\text{-X.C}_6\text{H}_4\text{-}$) has recently been published [93JCS(D)967] and shows that the 2^+ ring is reversibly reduced to the dithiadiazolyl radical 2^\cdot at potentials in the region +0.56 to 0.68 (versus SCE), depending upon the nature of the substituent X. A second irreversible process is also observed which has been attributed to formation of the dithiadiazolide anion 2^- . This reduction is irreversible due to reaction with the cation.



Although there is a close correlation [93JCS(D)967] between the half-wave reduction potentials of the $p\text{-X.C}_6\text{H}_4\text{—CN}_2\text{S}_2$ cations and the Hammett constant for the substituent X, the reaction constant ρ (which indicates the sensitivity of the electroactive species (2^+) to electronic effects) is very small. Such a low value of ρ (~ 0.1) can be considered to arise through the nature of the reduction process, i.e., partial filling of the 2^+ LUMO (Section III) which possesses a node at the heterocyclic ring carbon and thus limits (to a first approximation) conjugation with the substituent group (92IC442).

Although few redox potentials have been reported for other derivatives of 2^+ (but see 89JA9276), unpublished results (89TH1; 93UP2) suggest that most derivatives of 2^+ should lie, depending upon the nature of R, within the region +0.5 to +0.7 V.

Care should be taken when comparing and examining redox potentials for these cations since, although they appear to be temperature-independent [93JCS(D)967], $E_{1/2}(\text{red})$ values for the same cations can still vary. Such variations may arise through differences in counterion, supporting electrolyte, solvent, reference electrode, and salt bridge. Reduction potentials for the following $\text{PhCN}_2\text{S}_2^+$ salts in acetonitrile solution are tabulated, along with the supporting electrolyte:

Salt	Supporting electrolyte	Reduction potential	Reference
$[\text{Ph}\overline{\text{CNSSN}}][\text{AsF}_6]$	$[\text{TBA}][\text{AsF}_6]$	$E_{1/2}(\text{red}) = +0.50 \text{ V}$	89TH1
$[\text{Ph}\overline{\text{CNSSN}}][\text{AsF}_6]$	$[\text{TBA}][\text{BF}_4]$	$E_{1/2}(\text{red}) = +0.59 \text{ V}$	93JCS(D)967
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl}$	$[\text{TBA}][\text{AsF}_6]$	$E_{1/2}(\text{red}) = +0.61 \text{ V}$	89TH1
$[\text{Ph}\overline{\text{CNSSN}}][\text{PF}_6]$	$[\text{TBA}][\text{PF}_6]$	$E_{1/2}(\text{red}) = +0.68 \text{ V}^*$	89JA9276

* Versus Ag/AgCl.

D. ELECTRON SPIN RESONANCE SPECTRA

Dithiadiazolylium salts with "soft" anions (Section V.B–E), prepared via anion exchange (Section VI.A) or by oxidation of 2^+ (Section XI.A.2), frequently show considerable charge transfer from anion to cation. In some cases these charge-transfer salts are esr-active. For example, crystals of the charge-transfer complex $[\text{Ph}\overline{\text{CNSSN}}][\text{S}_3\text{N}_3]$ [90JCS(D)2793] have been found to be esr-active (89MRC1161). Although there was evidence for $[\text{Ph}\overline{\text{CNSSN}}]$, no esr signal was observed for the anticipated $\text{S}_3\text{N}_3^{\cdot-}$ radical (89MRC1161). The signal has been attributed to $[\text{Ph}\overline{\text{CNSSN}}]^{\cdot-}$ radicals which are adventitiously trapped in the host lattice and which take up the locations of $[\text{Ph}\overline{\text{CNSSN}}]^+$ cations. Charge-balance considerations dictate that the neutral radical $[\text{Ph}\overline{\text{CNSSN}}]^{\cdot-}$ impurity must be accompanied by a neutral replacement for $[\text{S}_3\text{N}_3^-]$, such as a solvent molecule or "hole" (89MRC1161). $[\text{Ph}\overline{\text{CNSSN}}][\text{S}_3\text{N}_3]$ is predominantly diamagnetic at room temperature, but shows a small superparamagnetic response when increasing the magnetic field (93UP3). This response is similar to those observed in dithiadiazolyl–metal complexes (Section XI.C) and some salts of the isomeric 1,3,2,4-dithiadiazolylium ring (Section XIV.C). Whether such magnetic response is attributable to spontaneous alignment of $[2]^{\cdot-}$ radicals or ferromagnetic impurities is currently open to debate. The esr spectra of $[2]^{\cdot-}$ radicals are described more fully in Section IX.A.

V. X-Ray Diffraction Studies of Mono-1,2,3,5-Dithiadiazolylium Salts

X-Ray diffraction studies have been carried out on a variety of 2^+ salts. There are five main types involving

- (A) "hard" noninteracting anions,
- (B) "soft" anions that interact in-plane,
- (C) "soft" anions that interact out-of-plane,
- (D) complex salts containing a mixture of anions of types (A), (B), and (C), and
- (E) partially reduced salts.

Such a wealth of structural data allows us to draw several conclusions about the nature of the dithiadiazolylium ring in the solid state.

A. 1,2,3,5-DITHIADIAZOLYLIUM SALTS OF HARD ANIONS

Although 2^+ salts are most commonly formed as the chloride, metathesis reactions (Section VI.A) allow a variety of other salts to be prepared readily. When studying the effect of partial or complete reduction on the geometry of the 2^+ heterocycle, it is useful to compare bond distances and angles with an "unperturbed" system [90JCS(D)2793], and this is best attained by examining salts of "hard" anions such as AsF_6^- , PF_6^- , and SbF_6^- , which show only weak secondary S . . . F interactions between cation and anion. To date, four salts of this type have been reported: two with aromatic substituents, $[\text{Ph}.\overline{\text{CNSSN}}][\text{AsF}_6]$ and $[p\text{-Cl.C}_6\text{H}_4.\overline{\text{CNSSN}}][\text{AsF}_6]$ [89CB1067; 92TH1], and two with nonaromatic substituents, $[\text{Cl}.\overline{\text{CNSSN}}][\text{AsF}_6]$ and $[\text{Me}_2\text{N}.\overline{\text{CNSSN}}][\text{SbF}_6]$ (83CB416; 89JA6147). In all four cations, the ring geometries (particularly bond angles) are remarkably similar (Table IV), indicating the small electronic effect of the substituent group on the dithiadiazolylium ring [see, e.g., electrochemical studies, Section IV.C; see also 93JCS(D)967]. In all cases the CN_2S_2 heterocyclic ring is planar (within experimental error), but for aryl derivatives coplanarity between aryl and heterocyclic rings is not always observed: the twist angle between the two rings varies between 0 and 40° , depending on the nature of R and also, as we shall see later (Sections V.B–E), on the anion. Perhaps these deviations from planarity arise largely through packing effects.

B. 1,2,3,5-DITHIADIAZOLYLIUM SALTS WITH ANIONS THAT INTERACT IN-PLANE

The first 2^+ salt to be studied by X-ray diffraction was $[\text{Cl}_3\text{C}.\overline{\text{CNSSN}}]\text{Cl}$ (77INCL143); it showed that the chloride anion is in the plane of the heterocyclic ring and roughly equidistant from the two sulfur atoms. Similar S---Cl interactions are observed for the analogous salts $[\text{Me}.\overline{\text{CNSSN}}]\text{Cl}$ [86ZAC(536)153], $[\text{Ph}.\overline{\text{CNSSN}}]\text{Cl}$ [88AX(C)1807], and $[p\text{-Cl.C}_6\text{H}_4.\overline{\text{CNSSN}}]\text{Cl}$ (93UP4). (In this last compound the three-center S---Cl (anion) interaction is augmented by weaker S . . . Cl interactions, still within the molecular plane.) Three-center S---Cl interactions are a common feature in halides of cationic 1,2-disulfur compounds, for instance, dithiolium halides (71ACS1567) and $[\text{S}_3\text{N}_2\text{Cl}]_2$ [84JCS(D)1377]. Since salts of $\text{S}_3\text{N}_2^{++}$ 1 with oxygen-containing anions, such as CF_3SO_3^- and ClS_2O_6^- [74INCL647; 80CB226; 92JCS(D)3097], also show S---X interactions, we might expect 2^+ salts of similar oxo-anions to interact in

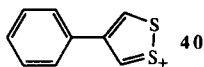
TABLE IV
HETEROCYCLIC BOND DISTANCES AND ANGLES FOR 1,2,3,5-DITHIADIAZOLYLIUM SALTS

Salt	Mean bond distance (Å)			Bond angle (°)			Reference
	C—N	N—S	S—S	NCN	CNS	NSS	
[Cl. $\overline{\text{CNSSN}}$][AsF ₆]	1.321(8)	1.573(5)	1.996(2)	120.3(5)	114.4(4)	95.4(2)	83CB416
[Me ₂ N. $\overline{\text{CNSSN}}$][SbF ₆]	1.353(10)	1.586(9)	2.022(7)	118.5(10)	115.6(9)	95.4(4)	89JA6147
[Ph. $\overline{\text{CNSSN}}$][Cl]	1.348(13)	1.592(10)	1.991(5)	118.7(8)	114.7(7)	95.6(3)	88AX(C)1807
[Ph. $\overline{\text{CNSSN}}$][AsF ₆]	1.345(6)	1.568(5)	2.023(2)	117.4(4)	116.2(4)	95.1(2)	89CB1067
[Ph. $\overline{\text{CNSSN}}$] ₂ [Pt(mnt) ₂]	1.343(14)	1.601(9)	2.050(4)	121.8(10)	113.7(8)	95.3(4)	94AX(C)28
[Ph. $\overline{\text{CNSSN}}$][Cl][S ₃ N ₂]	1.340(6)	1.616(5)	2.055(2)	120.6(5)	114.8(4)	94.9(2)	90JCS(D)2793
[Ph. $\overline{\text{CNSSN}}$] ₂ [Cl][S ₃ N ₃]	1.343(4)	1.605(3)	2.040(1)	119.8(1)	115.1(3)	95.1(1)	90JCS(D)2793
[Ph. $\overline{\text{CNSSN}}$][S ₃ N ₃]	1.344(8)	1.615(3)	2.064(2)	120.8(3)	114.8(3)	94.9(2)	90JCS(D)2793
[<i>p</i> -Cl.C ₆ H ₄ . $\overline{\text{CNSSN}}$][Cl]	1.336(6)	1.592(4)	2.007(3)	119.1(6)	115.1(4)	95.3(2)	93UP4
[<i>p</i> -Cl.C ₆ H ₄ . $\overline{\text{CNSSN}}$][AsF ₆]	1.341(9)	1.587(8)	2.010(5)	119.8(7)	114.5(6)	95.6(3)	92TH1
[<i>p</i> -Cl.C ₆ H ₄ . $\overline{\text{CNSSN}}$] ₂ [Pt(mnt) ₂]	1.323(16)	1.589(11)	2.001(8)	118.9(10)	115.5(9)	95.2(4)	94AX(C)28

an analogous manner. Although no oxo-anion salts have been characterized to date, RCN solvates of many dications (Sections XXII.C and XXIV.C) show similar nitrogen in-plane interactions with the dithiolium bridge. The radicals $[X.C_6H_4.C\bar{N}SSN]_2$, where $X = p\text{-Cl}$ and $m\text{-NC}$ (Section X.B.2) show similar in-plane $X \cdots S$ interactions. Thus the combination of a donor side group and a donor anion in salts of 2^+ can be expected to lead to a more complex array of interactions.

The shortening of the SS distance, associated with 3-center $S\cdots Cl$ interactions has been attributed to electron donation from the chlorine lone pair into an unoccupied orbital based on the heterocyclic ring [Section III; see also 90JCS(D)2793]. For instance, contrast the d_{SS} (2.023(2) Å) in the noninteracting salt $[Ph.C\bar{N}SSN][AsF_6]$ with d_{SS} (1.990(5) Å) in $[Ph.C\bar{N}SSN]Cl$. In the presence of further secondary bonding, the SS bond length tends to increase again; see, e.g., $[p\text{-Cl}.C_6H_4.C\bar{N}SSN][AsF_6]$ (2.010(5) Å) and $[p\text{-Cl}.C_6H_4.C\bar{N}SSN]Cl$ (2.007(3) Å).

The crystal packing in $[p\text{-Cl}.C_6H_4.C\bar{N}SSN]Cl$ is remarkably similar to that in the 1,2-dithiolium salt $[Ph.CC(H)SSCH]Cl$ [40]Cl (Fig. 5), which also shows similar $S \cdots Cl$ and $S\cdots Cl$ interactions (71ACS1567). Several other salts of this cation have been crystallized, e.g., [40]Br, [40]I, and [40][NCS] (interacting through nitrogen) (66ACS1874; 69ACS1082; 69ACS1367); and thus we might expect similar structures for analogous [2]X ($X^- = Cl^-, Br^-, I^-, SCN^-, \text{etc.}$) salts.



C. 1,2,3,5-DITHIADIAZOLYLIUM SALTS WITH ANIONS THAT INTERACT OUT-OF-PLANE

Several 2^+ salts (particularly where $R = Ph, p\text{-Cl}.C_6H_4$) have been prepared with soft anions that interact with the 2^+ π -system through a $\pi\text{-}\pi^*$ donor-acceptor process. Of these salts, $[Ph.C\bar{N}SSN][S_3N_3]$ [90JCS(D)2793] and $[Ph.C\bar{N}SSN]_2[Pt(mnt)_2]$ [94AX(C)28] have been characterized by X-ray crystallography. These two structures are shown in Figure 6.

In both $[Ph.C\bar{N}SSN][S_3N_3]$ and $[Ph.C\bar{N}SSN]_2[Pt(mnt)_2]$, there are π out-of-plane interactions between cation and anion, as previously described in Section III, and arising through π/π^* overlap. In order to maximize such overlap, the mean planes of cations and anions in both complexes are approximately coplanar and the twist angle between the phenyl and

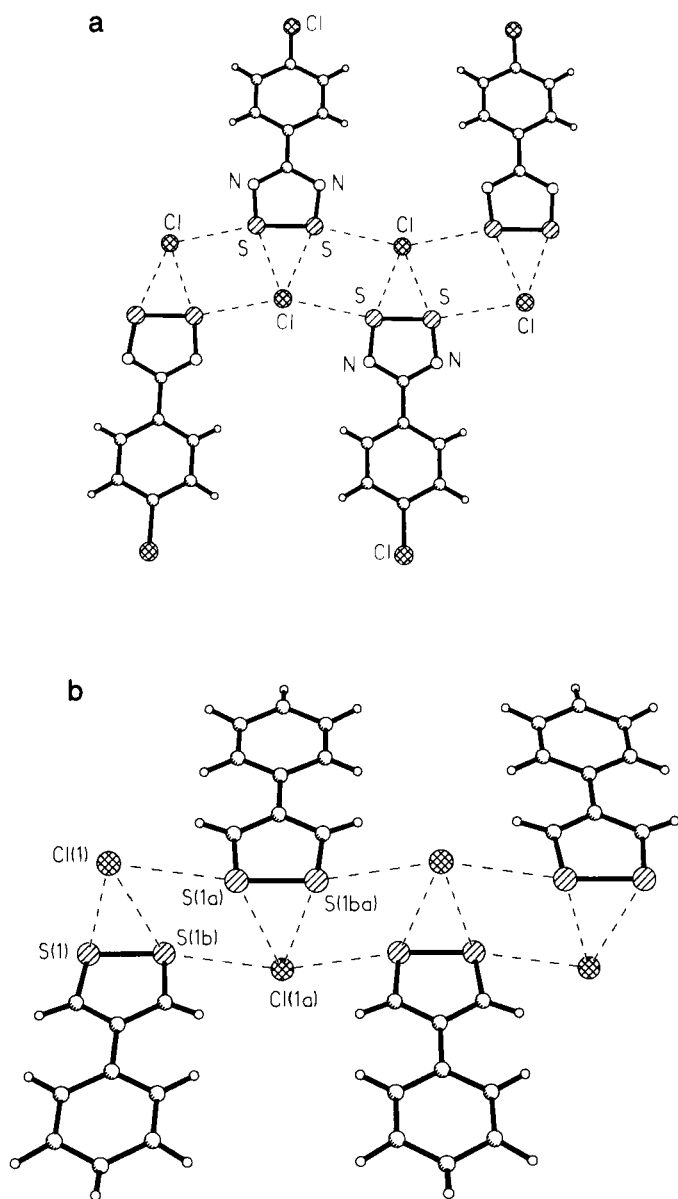


FIG. 5. Packing diagrams for (a) $[p\text{-Cl.C}_6\text{H}_4.\overline{\text{CNSSN}}]\text{Cl}$ and (b) $[\text{Ph}.\overline{\text{C}(\text{CH})\text{SS}(\text{CH})}]\text{Cl}$.

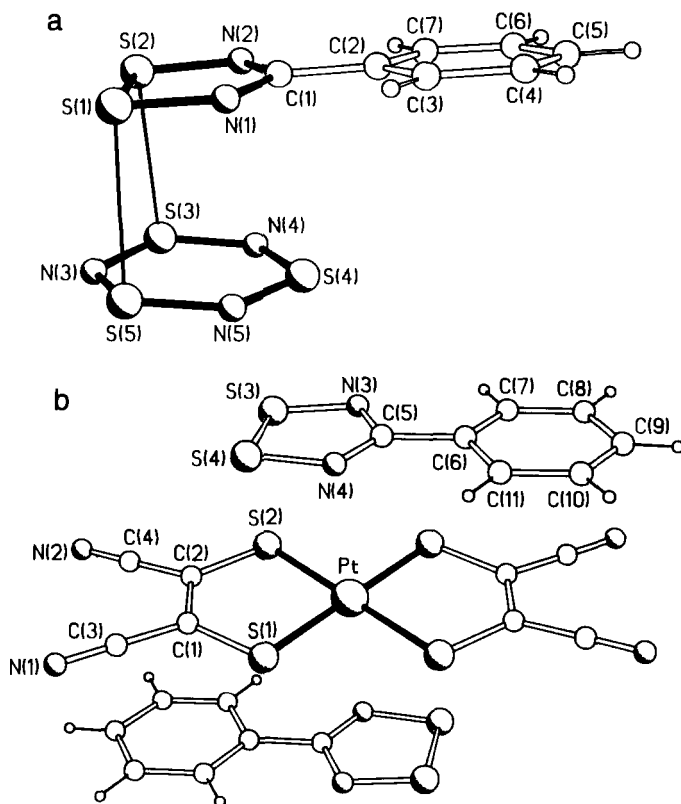


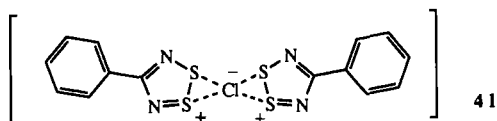
FIG. 6. Structures of (a) $[\text{Ph.CNSSN}][\text{S}_3\text{N}_3]$ and (b) $[\text{Ph.CNSSN}]_2[\text{Pt}(\text{mnt})_2]$.

dithiadiazolyl rings is very small. Some indication of charge transfer is given by (i) the mean cation–anion separation and (ii) the SS bond distance in the complex, compared with the noninteracting $[\text{R.CNSSN}][\text{AsF}_6]$ and with neutral $[\text{R.CNSSN}]_2$ molecules [90JCS(D)2793; 92TH1]. For instance, in $[\text{Ph.CNSSN}][\text{S}_3\text{N}_3]$, the cation–anion distance is 2.906 Å and $d_{\text{SS}} = 2.064(2)$ Å and the extent of charge transfer (from MO studies) has been calculated at $\sim 0.86e^-$ [90JCS(D)2793]. In comparison, for $[\text{Ph.CNSSN}]_2[\text{Pt}(\text{mnt})_2]$, where the cation–anion separation is larger (2.998 Å), the bond weakening caused by charge transfer is significantly less ($d_{\text{SS}} = 2.050(4)$ Å) [94AX(C)28].

D. 1,2,3,5-DITHIADIAZOLYLUM SALTS CONTAINING BOTH IN-PLANE AND OUT-OF-PLANE ANIONS

These salts can be considered to arise through a mixture of the above "structural types" A and B or B and C; i.e., they all contain a chloride anion and one (or more) anions which may be noninteracting or may interact through π - π^* overlap.

In salts of the B/C type, two 2^+ rings are held together through a central chloride anion, forming a large planar $[(2)_2\text{Cl}]^+$ cation **41** with a slightly asymmetric environment around the halide center [90JCS(D) 2793; 94AX(C)28]. The S---Cl contacts are somewhat longer (mean $d_{\text{S-Cl}}$ 2.962 Å) than in the corresponding 1:1 salt $[\text{Ph}.\overline{\text{CNSSN}}]\text{Cl}$ (2.906 Å) because the chloride anion is interacting with four sulfur centers rather than two.



In both $[\mathbf{41}][\text{S}_3\text{N}_3]$ (Fig. 7a) and $[\mathbf{41}][\text{Pt}(\text{mnt})_2]$, there are secondary, out-of-plane π - π^* interactions between cation and anion, although they would appear stronger in the former salt (cation-anion separation 3.056 Å and ~3.5 Å, respectively) in agreement with the analogous structures described in Section V.C.

In comparison, $[\text{Ph}.\overline{\text{CNSSN}}]_3[\text{AsF}_6]_2\text{Cl}$ and $[\text{Me}.\overline{\text{CNSSN}}]_5[\text{CoCl}_4]\text{Cl}_3$ show a mixed A/B-type structure [86ZAC(536)153; 89CB1067]. In $[\text{Ph}.\overline{\text{CNSSN}}]_3[\text{AsF}_6]_2\text{Cl}$ (Fig. 7b) the chloride anion is surrounded asymmetrically by three 2^+ cations, where the S---Cl contacts are, as expected, even longer than those observed in either $[\text{Ph}.\overline{\text{CNSSN}}]\text{Cl}$ or **41**. The AsF_6^- anions interact very weakly with the cations through S . . . F and H . . . F interactions. For $[\text{Me}.\overline{\text{CNSSN}}]_5[\text{CoCl}_4]\text{Cl}_3$ there is a series of interactions between S, Cl^- , and CoCl_4^{2-} .

E. PARTIALLY REDUCED 1,2,3,5-DITHIADIAZOLYLUM SALTS

The only partially reduced salts characterized by X-ray diffraction are $[\text{CF}_3.\overline{\text{CNSSN}}]_3\text{Cl}$ (85CB3781) and $[p\text{-Cl}.\text{C}_6\text{H}_4.\overline{\text{CNSSN}}]_3\text{Cl}$ (93UP4). Chemically, each heterocyclic unit can be considered as $2^{1/3+}$, although crystallographically (by examining the SS distances) the former compound can be considered to be $[\text{CF}_3.\overline{\text{CNSSN}}]\text{Cl}$ with two neutral

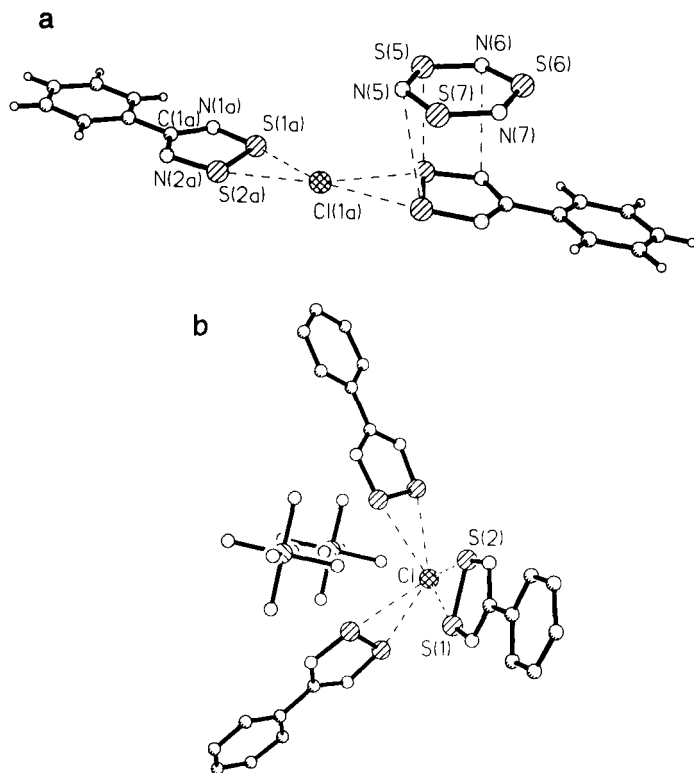


FIG. 7. Structures of (a) $[(\text{Ph}.\overline{\text{CNSSN}})_2\text{Cl}][\text{S}_3\text{N}_3]$ and (b) $[\text{Ph}.\overline{\text{CNSSN}}]_3\text{Cl}[\text{AsF}_6]_2$.

$[\text{cf}_3.\overline{\text{CNSSN}}]$ units interacting with the halide anion (Fig. 8a). In contrast, $[\text{p-Cl.C}_6\text{H}_4.\overline{\text{CNSSN}}]_3\text{Cl}$ shows similar SS bonds for all three heterocyclic rings, and this system can be considered as $[\mathbf{2}^{1/3+}]_3\text{Cl}$ (93UP4).

The compound $[\text{Ph}.\overline{\text{CNSSN}}][\text{s}_3\text{N}_2]\text{Cl}$ [89CC351; 90JCS(D)2793] (Fig. 8b) may also be expressed in terms of a type-E structure, although the $[\text{Ph}.\overline{\text{CNSSN}}]$ heterocycle formally carries no charge and can be considered to arise through association of $[\mathbf{1}]\text{Cl}$ and $\mathbf{2}$. However, there is significant π^*/π^* overlap between these units (separation of rings is 2.838 Å), and interactions between the chloride anion and both heterocycles (3.12 Å for $\text{Ph}.\overline{\text{CNSSN}}$ and 2.95 Å for s_3N_2) lead to deviations from coplanarity ($\theta = 26.2^\circ$). Such interactions between $\mathbf{2}'$ and Cl^- lead to the typical bond shortening of d_{SS} in $\mathbf{2}'$ (2.055 Å), such that the total system can be considered formally as $[\text{S}_6\text{N}_4.2\text{Ph}.\overline{\text{CNSSN}}]^{2+}[\text{Cl}^-]_2$, or $[\text{Ph}.\overline{\text{CNSSN}}]^{(\delta)+}[\text{S}_3\text{N}_2]^{(1-\delta)+}[\text{Cl}]^-$, where δ is <0.5 .

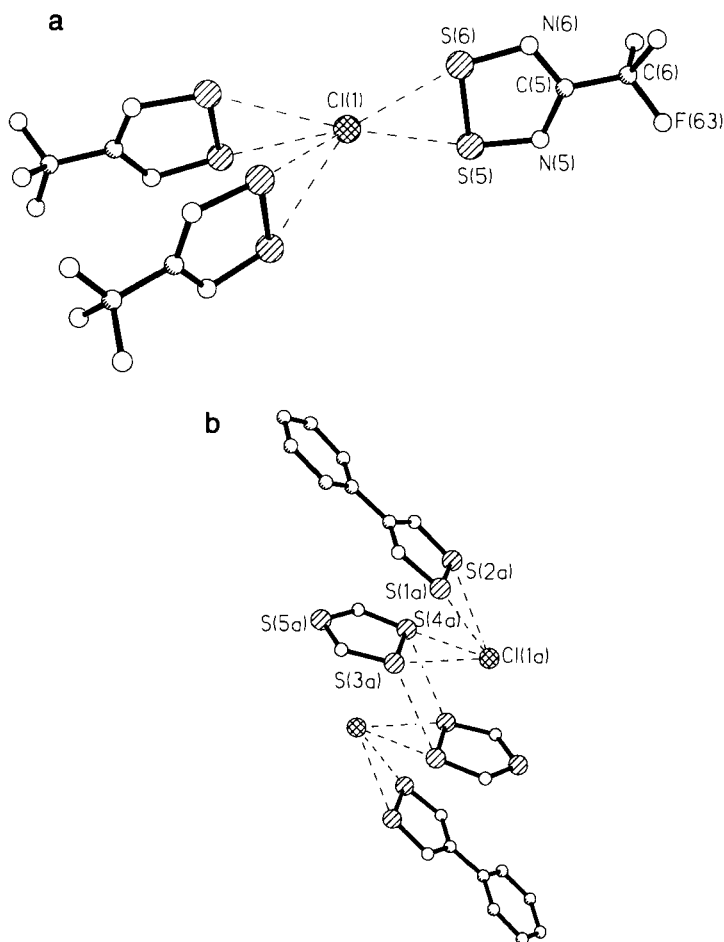


FIG. 8. Structures of (a) $[\text{CF}_3.\overline{\text{CNSSN}}]_3\text{Cl}$ and (b) $[\text{Ph}.\overline{\text{CNSSN}}][\text{S}_3\text{N}_2]\text{Cl}$.

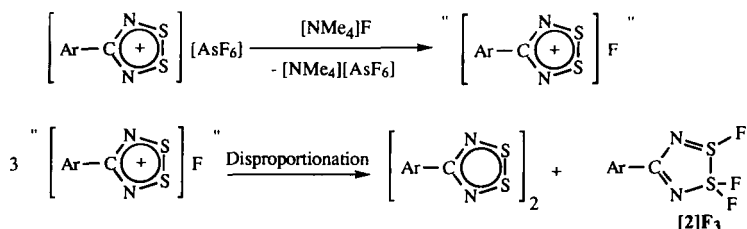
VI. Reactions of 1,2,3,5-Dithiadiazolylium Salts

A. METATHESIS AND ADDITION REACTIONS

The simplest reactions of dithiadiazolylium salts 2^+ are anion metathesis and reaction with Lewis acids. Since the majority of synthetic routes to 2^+ salts form $[2]\text{Cl}$, most subsequent reactions are also of $[2]\text{Cl}$. This is in sharp contrast to derivatives of 3^+ which are typically formed as the AsF_6^- salt (Section XII.A); consequently, there are some differences in

reaction types for the two isomeric dithiadiazolyls. Table V summarizes the different reagents and solvents employed.

Compounds fall broadly into two classes: those with 'hard' anions (Class A) and those with 'soft' anions (Classes B–E, Section V), which facilitate a larger degree of cation–anion interaction such as electron transfer. Indeed, in some cases the 3^+ salts of soft anions disproportionate in organic solvents [83JCS(P1)1181] with formation of the corresponding dithiadiazolyl radical $[3]^\cdot$ (see Section VII.A). There would appear to be one exception to this rule: reaction of $[\text{NMe}_4]\text{F}$ with an equimolar quantity of $[p\text{-Cl.C}_6\text{H}_4.\text{CNSSN}][\text{asf}_6]$ led to the isolation of $[p\text{-Cl.C}_6\text{H}_4.\text{CNSSN}]_2$ (93UP5), which appears to proceed via disproportionation of $[p\text{-Cl.C}_6\text{H}_4.\text{CNSSN}]\text{f}$. however, a perfluorinated product, such as $[2]\text{F}_3$, has yet to be characterized (see 39, Section II.D.5).



B. HYDROLYSIS

Both 1,2,3,5- and 1,3,2,4-dithiadiazolylum salts are susceptible to hydrolysis, although the ease of hydrolysis is affected by the solid-state structure and hence the counter-ion. Layered structures (Types B–D) with strong secondary interactions are remarkably resistant to hydrolysis [90JCS(D)2793], with some samples retaining their luster even after standing in water for 20 minutes. Class A salts tend to be more susceptible to hydrolysis, eventually yielding the amidine (IR spectrum), sulfur, and SO_2 .



C. REACTION WITH A NITROGEN PLASMA

This reaction will be described in more detail in Section (XI.B) since it was first observed for the radicals **2'** in the solid state. However, reaction

TABLE V
METATHESIS AND ADDITION REACTIONS OF 1,2,3,5-DITHIADIAZOLYLIUM SALTS

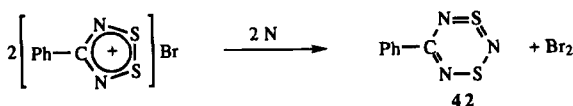
Reaction	Solvent	Yield ^a (%)	Product	Reference
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl} + \text{SbCl}_5$	CH_2Cl_2	42	$[\text{Ph}\overline{\text{CNSSN}}][\text{SbCl}_6]$	78CB2960
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl} + \text{SbCl}_5$	SOCl_2	—	$[\text{Ph}\overline{\text{CNSSN}}][\text{SbCl}_6]$	79JCS(P1)1192
$[\text{Cl}\overline{\text{CNSSN}}]\text{Cl} + \text{SbCl}_5$	<i>l.</i> SO_2	90	$[\text{Cl}\overline{\text{CNSSN}}][\text{SbCl}_6]$	83CB416
$[\text{Cl}_3\text{C}\overline{\text{CNSSN}}]\text{Cl} + \text{SbCl}_5$	SOCl_2	—	$[\text{Cl}_3\text{C}\overline{\text{CNSSN}}][\text{SbCl}_6]$	79JCS(P1)1192
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl} + \text{CF}_3\text{SO}_3\text{H}$	CH_2Cl_2	32	$[\text{Ph}\overline{\text{CNSSN}}][\text{CF}_3\text{SO}_3]$	78CB2960
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl} + \text{HN}(\text{SO}_2\text{F})_2$	CH_2Cl_2	34	$[\text{Ph}\overline{\text{CNSSN}}][\text{N}(\text{SO}_2\text{F})_2]$	78CB2960
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl} + [\text{Et}_3\text{O}][\text{BF}_4]$	CH_2Cl_2	45	$[\text{Ph}\overline{\text{CNSSN}}][\text{BF}_4]$	78CB2960
$[\text{Ph}\overline{\text{CNSSN}}]\text{Cl} + [\text{NO}][\text{PF}_6]$	CH_2Cl_2	55	$[\text{Ph}\overline{\text{CNSSN}}][\text{PF}_6]$	78CB2960
$[\text{CF}_3\overline{\text{CNSSN}}]\text{Cl} + [\text{CF}_3\overline{\text{CNSSN}}]_2$	<i>l.</i> SO_2	74	$[\text{CF}_3\overline{\text{CNSSN}}]_3\text{Cl}$	85CB3781
$[\text{FCNSSN}]\text{Cl} + \text{AgAsF}_6$	<i>l.</i> SO_2	88	$[\text{F}\overline{\text{CNSSN}}][\text{AsF}_6]$	85CB3781
$[\text{Cl}\overline{\text{CNSSN}}]\text{Cl} + \text{AgAsF}_6$	<i>l.</i> SO_2	96	$[\text{Cl}\overline{\text{CNSSN}}][\text{AsF}_6]$	83CB416
$[\textit{p}\text{-X}\cdot\text{C}_6\text{H}_4\overline{\text{CNSSN}}]\text{Cl} + \text{AgAsF}_6$	<i>l.</i> SO_2	70–97	$[\textit{p}\text{-X}\cdot\text{C}_6\text{H}_4\overline{\text{CNSSN}}][\text{AsF}_6]$	90JCS(D)2793
$[\text{Cl}\overline{\text{CNSSN}}]\text{Cl} + \text{HSO}_3\text{F}$	CH_2Cl_2	79	$[\text{Cl}\overline{\text{CNSSN}}][\text{SO}_3\text{F}]$	83CB416
$2 [\text{Cl}\overline{\text{CNSSN}}]\text{Cl} + \text{SnCl}_4$	<i>l.</i> SO_2	95	$[\text{Cl}\overline{\text{CNSSN}}]_2[\text{SnCl}_6]$	83CB416

2 [Ph. $\overline{\text{CNSSN}}$]Cl + SnCl ₄	SOCl ₂	—	[Ph. $\overline{\text{CNSSN}}$] ₂ [SnCl ₆]	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + FeCl ₃	SOCl ₂	89	[Ph. $\overline{\text{CNSSN}}$][FeCl ₄]	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + KBr	<i>l</i> .SO ₂	71	[Ph. $\overline{\text{CNSSN}}$]Br	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + [NH ₄][NCS]	<i>l</i> .SO ₂	71	[Ph. $\overline{\text{CNSSN}}$][NCS]	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + BCl ₃	<i>l</i> .SO ₂	—	[Ph. $\overline{\text{CNSSN}}$][BCl ₄]	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + NaOAc	<i>l</i> .SO ₂	—	[Ph. $\overline{\text{CNSSN}}$][OAc]	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + [PhCOO]Na	<i>l</i> .SO ₂	—	[Ph. $\overline{\text{CNSSN}}$][PhCOO]	79JCS(P1)1192
[Ph. $\overline{\text{CNSSN}}$]Cl + KI	<i>l</i> .SO ₂	—	[Ph. $\overline{\text{CNSSN}}$]I	79JCS(P1)1192
[Me ₂ N. $\overline{\text{CNSSN}}$]Cl + NOSbF ₆	PhCN	—	[Me ₂ N. $\overline{\text{CNSSN}}$][SbF ₆]	89JA6147
[Ph $\overline{\text{CNSSN}}$][AsF ₆] + [Pr ₄ N][S ₃ N ₃]	MeCN	57	[Ph $\overline{\text{CNSSN}}$][S ₃ N ₃]	90JCS(D)2793
2 [Ph $\overline{\text{CNSSN}}$]Cl + [Pr ₄ N][S ₃ N ₃]	MeCN	86	[(Ph. $\overline{\text{CNSSN}}$) ₂ Cl][S ₃ N ₃]	93UP2
2 [Ph. $\overline{\text{CNSSN}}$][AsF ₆] + [Et ₄ N] ₂ [Pt(mnt) ₂]	MeCN	75	[Ph. $\overline{\text{CNSSN}}$] ₂ [Pt(mnt) ₂]	94AX(C)28
[Ph. $\overline{\text{CNSSN}}$][AsF ₆] + [Et ₄ N][Pt(mnt) ₂]	MeCN	75	[Ph. $\overline{\text{CNSSN}}$][Pt(mnt) ₂]	94AX(C)28
[Ph. $\overline{\text{CNSSN}}$]Cl + [Et ₄ N][Pt(mnt) ₂]	MeCN	72	[Ph $\overline{\text{CNSSN}}$][Pt(mnt) ₂]	94AX(C)28
2[Ph. $\overline{\text{CNSSN}}$]Cl + [Et ₄ N][Pt(mnt) ₂]	MeCN	77	[(Ph. $\overline{\text{CNSSN}}$) ₂ Cl][Pt(mnt) ₂]	94AX(C)28
2[<i>p</i> -Cl.C ₆ H ₄ . $\overline{\text{CNSSN}}$]Cl + [Et ₄ N][Pt(mnt) ₂]	MeCN	79	[(<i>p</i> -Cl.C ₆ H ₄ . $\overline{\text{CNSSN}}$) ₂ Cl][Pt(mnt) ₂]	94AX(C)28
2[Ph. $\overline{\text{CNSSN}}$]Cl + [Ph $\overline{\text{CNSSN}}$] ₂	solid state	100	2[Ph $\overline{\text{CNSSN}}$] ₂ Cl	90JCS(D)2793

^a —, unspecified yield.

of some aryl-substituted dithiadiazolylum salts $[2]X$, particularly those with softer anions ($X = \text{Br}, \text{I}, \text{CN}, \text{S}_3\text{N}_3$) with a cool dc nitrogen plasma leads to reduction of the cation, followed by insertion of a nitrogen atom into the disulfide bond. In comparison to the reaction of **2**[•] with a nitrogen plasma, which cleanly yields **42**, nitrogenation of $[2]X$ leads to the loss of halogen (as Br_2 or I_2) or incorporation of the anion into a polymeric by-product [89JCS(D)1705]. Salts of harder anions do not undergo nitrogenation.

The dithiatriazene **42** can also be prepared by standard chemical techniques, particularly dechlorination of **23** (85JA7710).

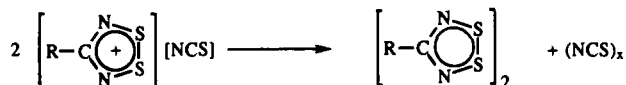


VII. Preparation of 1,2,3,5-Dithiadiazolyls

A. DISPROPORTIONATION OF 1,2,3,5-DITHIADIAZOLYLUM SALTS

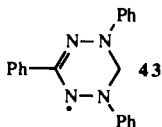
Certain dithiadiazolylum salts containing soft anions (particularly NCS^- and I^-) show a tendency to decompose on heating or on dissolution to give the corresponding dithiadiazolyls [80JCS(D)1812; 83JCS(P1)1181].

Surprisingly, $[p\text{-Cl.C}_6\text{H}_4.\text{CNSSN}]^+\text{f}$ (prepared in situ from equimolar amounts of $[p\text{-Cl.C}_6\text{H}_4.\text{CNSSN}][\text{asf}_6]$ and $[\text{NMe}_4]\text{F}$) decomposes to give the corresponding radical $[p\text{-Cl.C}_6\text{H}_4.\text{CNSSN}]^\bullet$; the driving force for this reaction appears to be disproportionation with formation of a more highly fluorinated material (93UP5) (see Section VI.A). Although this material was not isolated, similar perfluorinated materials, such as $\text{CF}_2(\text{N}=\text{SF}_2)_2$, have been described by Mews and co-workers as the product of fluorination of other dithiadiazolylum species (85CB3781) (Section II.C.5).



B. REDUCTION OF 1,2,3,5-DITHIADIAZOLYLUM SALTS

The first dithiadiazolyl radicals were prepared by reduction of dithiadiazolylum chloride salts using sodium dust, triphenylverdazyl **43**, or tetramethyl-*p*-phenylene diamine (82TL761).



Subsequently, other materials including zinc/copper couple, potassium, mercury, and elemental zinc were used [83JCS(P1)1181; 89JCS(D)1705; 92CJC919]. The reductions proceed smoothly at room temperature in oxygen-donor solvents such as THF or monoglyme [82TL761; 83 JCS(P1)1181] or in liquid SO_2 [85CB3781; 89JA1180; 89JA6147; 89 JCS(D)1705]. Purification of the crude product is usually carried out by vacuum sublimation, and this method frequently provides crystalline material suitable for X-ray diffraction studies [80JCS(D)1812; 89JA6147; 89JCS(D)1705; 92CJC919; 92IC1802; 93UP6, 93UP7]. Other reducing agents that have been employed include NaNCS , KCN , LiN_3 , PhMgBr , $n\text{BuLi}$, SnCl_2 [83JCS(P1)1181], and particularly Ph_3Sb (89JA1180; 92 CJC919; 92IC1802). In some of these cases reduction occurs via disproportionation (Section VII.A). Electrochemical reduction may also be used (93UP8).

C. REARRANGEMENT OF 1,3,2,4-DITHIADIAZOLYL RADICALS

The preparation of 1,2,3,5-dithiadiazolyl radicals by rearrangement of the isomeric 1,3,2,4-dithiadiazolyl radicals in solution [86CC140; 87CC69; 92JCS(D)1277] will be described more fully in Section XXI.A.1. In the case of some multi-1,2,3,5-dithiadiazolyl radicals, this reaction occurs in the solid state on thermolysis (Section XXIII.G.3). However, this route is not a common preparative technique, since these radicals are more conveniently prepared by direct reduction of 2^+ salts, as described in Section VII.B.

VIII. Theoretical Studies of 1,2,3,5-Dithiadiazolyl Radicals

Reduction of 2^+ to form 2^\cdot proceeds via the partial occupancy of the $\pi^* 2a_2$ orbital of 2^+ (Section III) and is accompanied by some modification of the frontier orbital energies, particularly $2b_1$ and $4b_2$, which become particularly close in energy. EHMO calculations by Jørgensen indicated $2b_1$ to be higher in energy than $4b_2$ [91JCS(D)1105] (a revision of that found in earlier work [89JCS(D)2229]).

Molecular orbital (MNDO) calculations have also been carried out by

Mews and co-workers to examine the energy barrier to rotation between cis, trans, and staggered arrangements of dithiadiazolyl units in dimeric $(\text{RCNSSN})_2$ (85CB3781). As described in Section X, these radicals have been found to take up a variety of configurations, depending on the substituent R. The calculations show that the energy difference between staggered (Section X.B.1, Fig. 12) and eclipsed (Section X.B.2, Fig. 13) configurations is small (~ 5 kJ/mol) while the difference between eclipsed and trans-oid forms is "very small." Consequently, the type of bonding becomes highly dependent on the substituent group and also on packing effects. As will be seen later (Section X), sterically crowded materials assume a twisted configuration, while planar substituents allow the slightly preferred cis-oid geometries [except for $(m\text{-NC}_6\text{H}_4\text{CNSSN})_2$, which takes up a trans-oid configuration (Section X.B.3, Fig. 15)]. The calculations also show how dimer stability varies as a function of distance between the two radical rings $2'$; in an eclipsed configuration the energy reaches a minimum at ~ 3.31 Å, while the trans-oid configuration allows closer approach at 2.97 Å. Experimentally (Section X) both cis-oid and trans-oid geometries have similar S . . . S bonding distances between rings with d_{SS} in the region 3.04–3.14 Å, consistent with the low energy differences involved.

The SOMO, of $2a_2$ symmetry, possesses a node at carbon but has high spin densities at both sulfur and nitrogen. The esr data (Section IX.A) typically show a simple 1 : 2 : 3 : 2 : 1 pentet due to coupling to two equivalent nitrogen nuclei ($I = 1$). Coupling to sulfur has also been observed in some cases (the low intensity is due to the low isotopic abundance of ^{33}S), and this coupling can be related to the spin density distribution of the $2a_2$ orbital [86JCS(D)1465]. Coupling to substituent nuclei is usually very small and not often directly observed, consistent with localization of the spin density on the heterocyclic ring. However, in some cases, particularly when fluorine atoms are closely bonded to the heterocycle (e.g., where $\text{R} = \text{F}$, CF_3 or C_6F_5), such coupling is observed; in this case it is the *ortho*-fluorine atoms that have the largest coupling constants (93MRC1027; 93UP9).

Open-shell calculations have also been carried out on derivatives of $2'$ in order to compare their calculated and experimental ionization potentials (Section IX.B) (89JA1181). Although Koopman's theorem (69IJMS419) proposes an absolute correspondence between the orbital energies and the ionization potentials, it is not observed in this case; the first ionization potentials are consistently some 1.5–2 eV too high. This is discussed more fully in Section IX.B.

Thus MO calculations have, to date, allowed qualitative comparisons between theoretical and experimental data and have been used to predict the nature of the frontier orbitals.

IX. Physical Properties of 1,2,3,5-Dithiadiazolyl Radicals

A. ELECTRON SPIN RESONANCE SPECTRA

In the solid state 1,2,3,5-dithiadiazolyls are present largely as spin-paired oligomers but with some radical monomer present. In solution there is an equilibrium between monomer and dimer; at room temperature the dimers are virtually completely dissociated. Variable-temperature esr studies have allowed some thermodynamic data to be determined for the monomer-dimer equilibrium in solution [86JCS(D)1465; 87CC69]. Esr spectra of 1,2,3,5-dithiadiazolyl radicals have been used extensively as a method of characterization; solution esr spectra typically show a 1 : 2 : 3 : 2 : 1 pentet due to coupling of the unpaired electron to two equivalent nitrogen ($I = 1$) nuclei ($a_N \sim 0.5$ mT). Although coupling to sulfur is large ($a_S \sim 0.6$ mT), the low abundance of ^{33}S means that this is frequently not observed. The isotropic g -value is typically in the region 2.01, similar to that of the free electron. Table VI summarizes the minor variations in g_{iso} and a_N for these radicals. In some cases hyperfine coupling to alkyl or aryl substituents is also observed—particularly for alkyl protons, fluorines, or *ortho*-fluorinated aryl derivatives. The esr spectrum of $\text{C}_6\text{F}_5\text{.CNSSN}^\cdot$ is illustrated in Figure 9. As expected, there is a decrease in a_F with increased bond distance between the fluorine atoms and the dithiadiazolyl ring: $a_F = 1.01$ mT (F.CNSSN^\cdot), 0.162 mT ($\text{F}_3\text{C.CNSSN}^\cdot$), and 0.161 mT (coupling to *ortho*-fluorines in $\text{C}_6\text{F}_5\text{.CNSSN}^\cdot$).

TABLE VI
ISOTROPIC ESR DATA FOR SUBSTITUTED 1,2,3,5-DITHIADIAZOLYL RADICALS
(ALL COUPLING CONSTANTS IN MILLI-TESLAS)

Substituent	T (K)	Solvent	g	a_N	a_H	a_F	a_{S-33}	Reference
Ph	298	$\text{C}_6\text{H}_6/\text{THF}$	2.0104	0.49				82TL761
Ph	205	d_8 -toluene	2.01019	0.517	~ 0.02		0.617	86JCS(D)1465
C_6F_5	219	d_8 -toluene	2.01012	0.505		0.161	0.678	93MRC1027
F	298	liquid SO_2		0.506		1.01		85CB3781
Cl	298	liquid SO_2		0.53				85CB3781
Br	298	liquid SO_2		0.5				85CB3781
I	298	$\text{SO}_2/\text{CFCl}_3$	2.0106	0.50				86CC140
Me	203	d_8 -toluene	2.0104	0.538	0.205		0.645	86JCS(D)1465
CF_3	193	d_8 -toluene	2.00939	0.490		0.162	0.679	93MRC1027
CF_3	298	liquid SO_2		0.51				85CB3781
CCl_3	298	$\text{C}_6\text{H}_6/\text{THF}$	2.0104	0.49				82TL761
<i>t</i> Bu			2.0121	0.52				87CC69
<i>t</i> Bu	203	d_8 -toluene	2.01059	0.510	~ 0.05		0.617	92MRC666

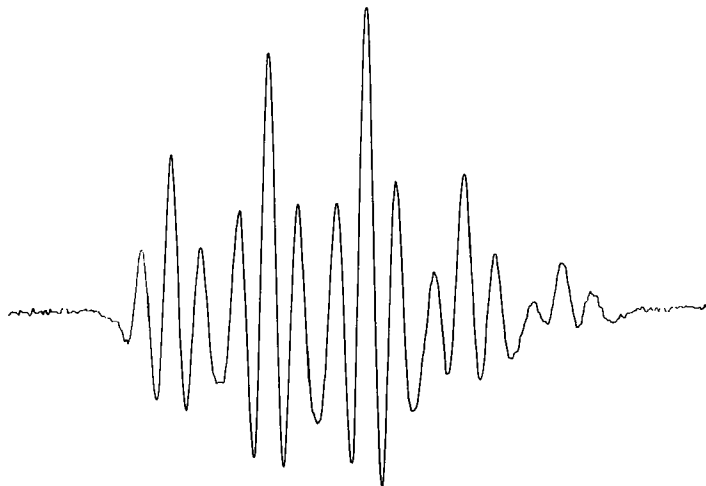


FIG. 9. Second derivative X-band esr spectrum of $[\text{C}_6\text{F}_5.\overline{\text{CNSSN}}]$ in d_8 -toluene at 219K.

The spin concentration in the nitrogen p -orbitals of $2'$ ($\text{R} = \text{Ph}$) has been estimated at 22.5% per nitrogen atom (94MRC487), significantly higher than for the analogous radical $1'$ (at 16%). Since the SOMO of $2'$ is of a_2 symmetry (Section VIII), we expect only small spin populations on the ring carbon (88CJC1299); therefore we may expect significant spin density on the sulfur atoms, as evidenced by the low values of a_{N} (in comparison to N -alkoxy-aryl-aminyls and N -alkylthio-aryl-aminyls) at ~ 1 mT in $\text{CF}_3.\overline{\text{CNSSN}}$ at low temperatures [86JCS(D)1465; 93MRC1027]. The isotropic sulfur coupling constants are greatest for the fluorinated derivatives of $2'$, and it would therefore appear that the use of fluorinated substituents increases the unpaired electron density at sulfur and decreases it at nitrogen. Variable-temperature esr studies have allowed some thermodynamic data to be determined for the monomer-dimer equilibrium in solution (93MRC1027).

Frozen solutions, i.e., matrices of $2'$, are also esr-active and show anisotropic esr spectra similar to those observed for many solid-state samples [86JCS(D)1465; 89MRC1161; 92MRC666; 93MRC1027]. Solid-state samples of these radicals are predominantly diamagnetic due to a spin-paired interaction between radical centers [83JCS(P1)1181; 85CB3781] (Section X), comparable to the dimerization of 1 [83JCS(P1)1181]. Nevertheless, since the dimerization energy (outlined above) is small for the majority of $2'$ derivatives, these materials are also esr-active in the solid state [83JCS(P1)1181; 84CJC1124; 86JCS(D)1465]. In contrast, crystalline samples of $(\text{C}_6\text{F}_5.\overline{\text{CNSSN}})_2$ are esr-inactive since

the electron pairing in this system is significantly stronger than in other derivatives of **2'** (93MRC1027), although anisotropic data can be determined from frozen glass spectra. The solid-state esr spectra of **2'** exhibit anisotropic *g*-values and coupling constants. The smallest *g*-tensor is perpendicular to the ring plane and possesses the largest hyperfine coupling constant; this is consistent with the unpaired electron being localized in a π -based molecular orbital (89MRC1161). Table VII shows the anisotropic data for some of these radicals in the solid state and/or frozen solution.

B. PHOTOELECTRON SPECTRA

The ultraviolet photoelectron (UPS) spectra of several 1,2,3,5-dithiadiazolyl radicals ($R = CF_3, Cl, Ph, Me_2N$) have been studied (89JA1180; 89JA6147) in order to compare the ionization potentials of the radicals—and, in the last case, the corresponding cation **2⁺** ($R = Me_2N$)—with values obtained from MO calculations. The photoelectron spectra show three distinct regions: 7–9 eV, ionization of electrons from the SOMO of **2'**; at higher energy, ionization of heterocyclic σ and π electrons; and finally ionization from the substituent group. The UPS spectrum of **2'** ($R = Cl$) shown in Figure 10 is marked with its assignments (89JA1180).

Such UPS data offer a unique opportunity to compare experimental data and MO calculations on the nature of the molecular orbitals, including ground state and both singlet and triplet excited states. Although the ionization potentials determined from MO calculations were not exact, relative energies were in good agreement with the theoretical values (Sections III and VIII).

C. CONDUCTIVITY

Haddon proposed that molecular conductors could be prepared from neutral, rather than charged radicals [75AJC2343; 75N(L)(256)394]. Polymeric arrays of such radicals (see Fig. 11) would facilitate greater conductivity and reduce susceptibility to Peierls distortion. Dithiadiazolyl radicals and their selenium analogs (92IC1802) are particularly attractive building blocks because the nodal plane of the SOMO limits spin leakage onto the group attached at carbon. Furthermore, modification of the substituent on **2'** should allow intrastack interactions to be maximized and interstack interactions to be minimized, thus minimizing Peierls distortions.

These physical properties are highly dependent on the nature of the

TABLE VII
ANISOTROPIC ESR DATA FOR 1,2,3,5-DITHIADIAZOLYL RADICALS AS SOLIDS OR FROZEN SOLUTIONS
(ALL COUPLING CONSTANTS IN MILLI-TESLAS)

Radical	Me. $\cdot\overline{\text{CNSSN}}\cdot$	Ph. $\cdot\overline{\text{CNSSN}}\cdot$	Ph. $\cdot\overline{\text{CNSSN}}\cdot$	<i>t</i> Bu. $\cdot\overline{\text{CNSSN}}\cdot$	CF ₃ . $\cdot\overline{\text{CNSSN}}\cdot$	C ₆ F ₅ . $\cdot\overline{\text{CNSSN}}\cdot$
Temperature (K)	112	109	77	203	123	123
State	<i>d</i> ₈ -toluene glass	<i>d</i> ₈ -toluene glass	[Ph $\cdot\overline{\text{CNSSN}}\cdot$][S ₃ N ₃]	<i>d</i> ₈ -toluene glass	<i>d</i> ₈ -toluene glass	<i>d</i> ₈ -toluene glass
<i>g</i> _{xx}	2.0026	2.0021	2.0011	2.0020	2.0009	2.0025
<i>g</i> _{yy}	2.0090	2.0078	2.0075	2.0082	2.0064	2.0085
<i>g</i> _{zz}	2.0215	2.0218	2.0197	2.0211	2.0200	2.0220
<i>a</i> _{Nxx}	1.43	1.410		1.407	1.350	1.384
<i>a</i> _{Nyy}	0.08	0.107		0.036	0.004	0.157
<i>a</i> _{Nzz}	0.11	0.035		0.036	0.036	0.121
<i>a</i> _{Hxx}	0.242					
<i>a</i> _{Hyy}	0.242					
<i>a</i> _{Hzz}	0.242					
<i>a</i> _{Fxx}					0.189	0.157
<i>a</i> _{Fyy}					0.139	0.157
<i>a</i> _{Fzz}					0.203	0.232
Reference	86JCS(D)1465	86JCS(D)1465	89MRC1161	92MRC666	93MRC1027	93MRC1027

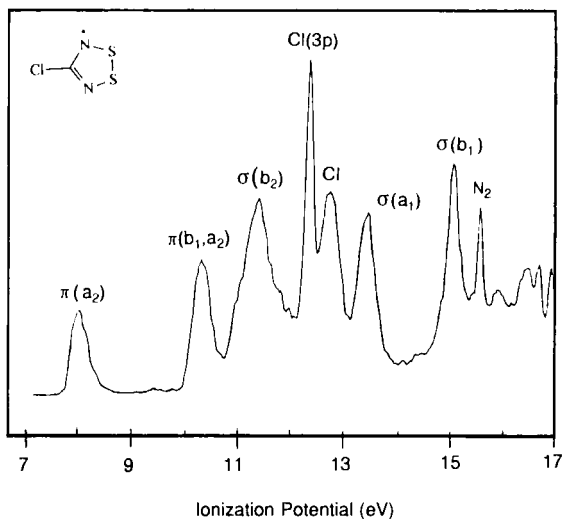


FIG. 10. UPS spectrum of $[\text{Cl.CNSSN}]^+$ (Reproduced in an amended version with kind permission from 89JA1180. Copyright 1989 American Chemical Society.)

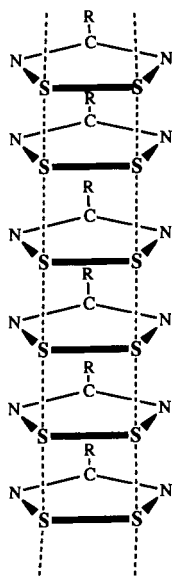


FIG. 11. Idealized molecular packing for conductivity in dithiadiazolyls.

molecular packing and hence the substituent group. Consequently, in order to maximize conductivity, the factors affecting molecular packing need to be thoroughly investigated and understood. Although this has not yet been achieved, significant advances have been made in recent years and are described in Section X.B. The majority of 1,2,3,5-dithiadiazolyl radicals form discrete dimeric pairs and are insulators. However, Oakley and co-workers recently found that $[m\text{-NC}_6\text{H}_4\text{.}\dot{\text{C}}\text{NSSN}]_2$ forms a stacking pattern similar to that shown in Figure 11; the radical units are not evenly spaced, but rather possess sets of alternate long (4.26 Å) and short (3.13 Å) bonding interactions between rings. Although the conductivity of this material was not reported, the conductivity of the isomorphous selenium analog was only $\sim 10^{-9}$ S/cm at room temperature, but rose to 10^{-5} S/cm around 450K. In order to improve the intrastack interactions (i.e., increase orbital overlap), a series of multidithiadiazolyls were prepared. Their structures and physical properties are described in Section XXII.E and F.

D. MAGNETISM

Dithiadiazolyls are usually associated in the solid state through spin-paired interactions (Section X.B) and are thus predominantly diamagnetic. However, as previously mentioned (Section IX.A), these materials do tend to possess a small number of paramagnetic sites, depending on the degree of crystallinity and the strength of bonding between monomeric units. For example, crystalline samples of the strongly associated derivative $[\text{C}_6\text{F}_5\text{.}\dot{\text{C}}\text{NSSN}]_2$ are esr-silent (93MRC1027), whereas samples of $[\text{Ph.}\dot{\text{C}}\text{NSSN}]_2$ are esr-active (Section IX.A) [86JCS(D)1465]. On warming, the number of paramagnetic sites increases due to breaking of the weak bonds between $2'$ units. Such an increase in radical centers leads to an increase in magnetic susceptibility. Eventually, dissociation is so great that the liquid state is formed. For many alkyl derivatives (e.g., $t\text{Bu.}\dot{\text{C}}\text{NSSN}$), this may occur below or near room temperature since the bonding energy is weakened through steric bulk.

In the liquid phase, these radicals are strongly paramagnetic, and they belong to a rare class of "paramagnetic liquids" (87CC69). For $t\text{Bu.}\dot{\text{C}}\text{NSSN}$, the effective magnetic moment has been calculated at $1.4 \mu_B$ at 20°C, slightly less than that expected for noninteracting $S = \frac{1}{2}$ monomers (87CC69). Variable-temperature solution esr measurements on this material show that this low value is unlikely to be caused by a dimerization or oligomerization process since the high percentage of monomer implies a positive $\Delta G^\circ_{\text{dim}}$ value at room temperature (caused by a large

entropy term, ΔS°) (Section IX.A). The low magnetic moment must therefore be attributable to some other spin-pairing mechanism (87CC69).

X. Electron and X-Ray Diffraction Studies of 1,2,3,5-Dithiadiazolyl Radicals

A. ELECTRON DIFFRACTION STUDIES

Electron diffraction studies on **2'** ($R = CF_3$) (85CB3781) indicate that, in the gas phase, $CF_3\cdot\bar{C}N\bar{S}S\bar{N}$ is not associated (comparable to **2'** in solution, Section IX.A); the ring is planar and the CF_3 substituent has a negligible barrier to rotation about the C—C bond.

B. X-RAY DIFFRACTION STUDIES

Several X-ray structures of derivatives of **2'** have been determined. In the initial studies there was special interest in how the modes of association in the solid state compare with the monomeric structures in solution and in the gas phase. More recently, structural studies have been more concerned with the factors affecting molecular packing. Ordered polymeric arrays of dithiadiazolyl radicals have been proposed as potential conducting materials (Section IX.C). The types of structure found so far are outlined below, together with a discussion of the factors thought to affect the molecular packing. Table VIII shows the mean heterocyclic bond distances and angles and the secondary S . . . S contacts linking monomers for all three structural types outlined below.

1. *Twisted Configurations*

In cases where the radical functionality possesses nonplanar substituents, e.g., $(CF_3\cdot\bar{C}N\bar{S}S\bar{N})_2$ (85CB3781), $(Me\cdot\bar{C}N\bar{S}S\bar{N})_2$ [89JCS(D)1705], $(Me_2N\cdot\bar{C}N\bar{S}S\bar{N})_2$ (89JA6147), and $(tBu\cdot\bar{C}N\bar{S}S\bar{N})_2$ (88TH1), the radicals take up twisted configurations (within the dimer) and this minimizes steric repulsions. The monomer units are held together through one strong S . . . S contact ($2.997 \leq d_{SS} \leq 3.108$) and some weaker S . . . N interactions (Fig. 12a). Further interactions between dimers lead to a complex network, as exemplified by $(CF_3\cdot\bar{C}N\bar{S}S\bar{N})_2$ (Fig. 12b). Such steric crowding tends to make these materials low-melting solids or liquids at room temperature, e.g., $(tBu\cdot\bar{C}N\bar{S}S\bar{N})_2$, m.p. 22°C.

TABLE VIII
HETEROCYCLIC BOND DISTANCES, ANGLES, AND INTERMOLECULAR SULFUR–SULFUR DISTANCES FOR 1,2,3,5-DITHIADIAZOLYLS

Dithiadiazolyl substituent	Bond distance (Å)			Dimer separation	Bond angle (°)			Reference
	C—N	N—S	S—S	S . . . S	NCN	CNS	NSS	
Twisted								
Me ₂ N	1.348(2)	1.627(2)	2.080(1)	3.036(1)	122.4(2)	113.8(1)	94.99(6)	89JA6147
CF ₃	1.318(7)	1.630(5)	2.087(2)	2.988(2)	126.1(5)	112.4(4)	94.6(2)	85CB3781
Me	1.324(5)	1.636(3)	2.076(2)	3.097(3)	122.2(4)	114.5(3)	94.5(1)	89JCS(D)1705
<i>t</i> Bu	1.33(1)	1.62(2)	2.079(5)	3.073(5)	121(2)	115.4(8)	94.2(5)	89TH1
Cis-oid								
Ph	1.33	1.63	2.089	3.102	121	116	94.1	80JCS(D)1812
<i>p</i> -Cl.C ₆ H ₄	1.333(5)	1.634(3)	2.085(2)	3.099	123.3(3)	113.7(3)	94.6(1)	93UP5
<i>p</i> -MeS.C ₆ H ₄	1.346(6)	1.641(4)	2.097(2)	3.061	121.7(4)	114.7(3)	94.5(1)	93UP6
<i>p</i> -NC.C ₆ H ₄	1.33	1.63	2.081(1)	3.10(2)	23.1	113.8	94.6	92IC1802
α - <i>m</i> -NC.C ₆ H ₄	1.33	1.63	2.080(3)	3.13(2)	123.0	113.9	94.6	92IC1802
2-cyano-furyl	1.327	1.638	2.077	3.126	125.1	112.6	94.5	92CJC919
C ₆ F ₅	1.338	1.640	2.097(1)	3.067	124.1(2)	113.2	94.7	93UP7
Trans-oid								
β - <i>m</i> -NC.C ₆ H ₄	1.335	1.626	2.087	3.141(1)	122.9	114.0	94.6	92IC1802
Monomeric								
<i>p</i> -NC.C ₆ F ₄	1.327(2)	1.638(2)	2.0897(14)	4.613 ^a	123.9(2)	113.61(13)	94.43(8)	93UP10

^a Closest in-plane S . . . S contact is 3.601 Å.

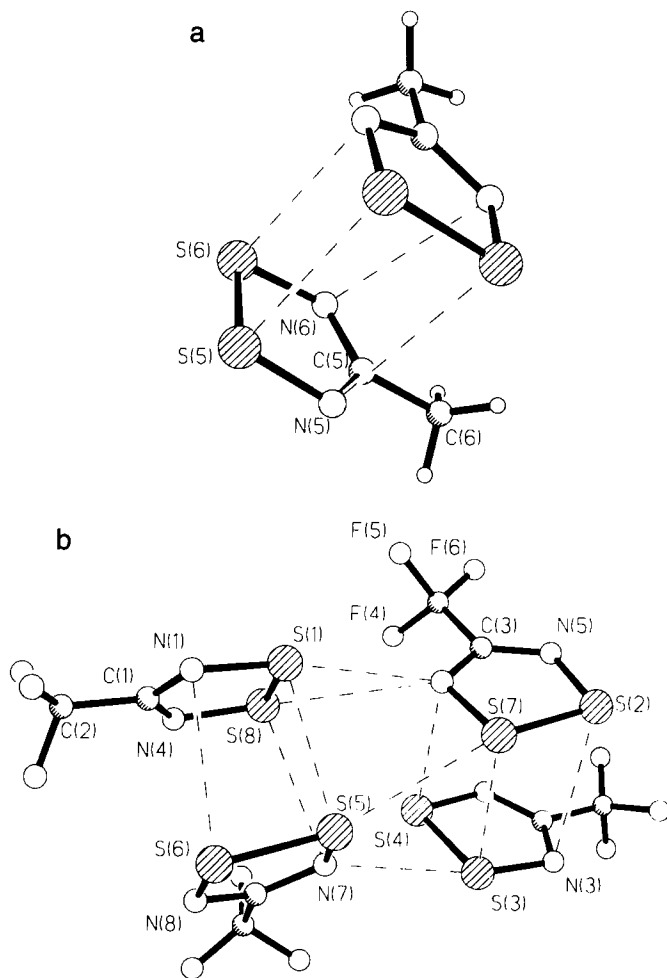


FIG. 12. (a) Structure of $[\text{Me}.\overline{\text{CNSSN}}]_2$ and (b) secondary interactions in $[\text{CF}_3.\overline{\text{CNSSN}}]_2$.

2. *Cis-oid Configurations*

The great majority of dithiadiazolylys studied have planar substituents, particularly aryl derivatives, i.e., $(\text{Ph}.\overline{\text{CNSSN}})_2$ [80JCS(D)1812], $(p\text{-Cl}.\text{C}_6\text{H}_4.\overline{\text{CNSSN}})_2$ (93UP5), $(m\text{- and } p\text{-NC}.\text{C}_6\text{H}_4.\overline{\text{CNSSN}})_2$ (92IC1802), $(p\text{-MeS}.\text{C}_6\text{H}_4.\overline{\text{CNSSN}})_2$ (93UP6), $(\text{C}_6\text{F}_5.\overline{\text{CNSSN}})_2$ (93UP7), and the furanyl derivative, $(4\text{-NC}.\text{C}_4\text{H}_2\text{O}.\overline{\text{CNSSN}})_2$ (92CJC919). In the solid state these materials form dimeric pairs which are held together through two

S . . . S interactions, leading to a cis-oid configuration of aryl substituents about the heterocyclic rings (Fig. 13a). The nature of the four-center, two-electron bonding interaction (Section VIII) leads, on the whole, to slightly longer (more delocalized) but, as it is twofold, significantly stronger bonding between individual monomer units, with $3.10 \leq d_{SS} \leq 3.13$. This stronger bonding is illustrated by the lower volatility of these materials (which are typically sublimed *in vacuo* at $\sim 100^\circ\text{C}$), e.g., (*p*-Cl.C₆H₄. $\overline{\text{CNSSN}}$)₂, m.p. 115°C [89JCS(D)1705].

Although their molecular structures are remarkably similar, the crystal habits of many of these radical pairs differ significantly. Such modification of molecular packing is of vital importance in the development of the polymeric arrays of radicals, as described in Section IX.C. The parent radical (Ph. $\overline{\text{CNSSN}}$)₂ does not exhibit the idealized one-dimensional array, but recent results (92IC1802; 93UP5; 93UP6; 93UP7) have shown that minor modification of the aryl substituent (see below) leads to significantly different molecular packing. The structure of (*p*-Cl.C₆H₄. $\overline{\text{CNSSN}}$)₂ shows similarities to those of [2]Cl (R = Ph) (Section V.B); the three-center interaction between two sulfur atoms and the anion is replaced by appreciable in-plane S . . . Cl interactions between the disulfide bridge of one dithiadiazolyl and the Cl substituent from a second dimer. (Since van der Waals radii are, in general, shorter along than perpendicular to the bond direction [85AX(B)274], S . . . Cl secondary distances are likely to be shorter when in the plane of the ring, i.e., along the C—Cl vector). Similar secondary interactions between the disulfide bridge and substituents bearing lone pairs are also observed in other structures, e.g., (MeS.C₆H₄. $\overline{\text{CNSSN}}$)₂ (Fig. 13b) and (C₆F₅. $\overline{\text{CNSSN}}$)₂. The cyano derivatives (*m*- and *p*-NC.C₆H₄. $\overline{\text{CNSSN}}$)₂ again show secondary interactions

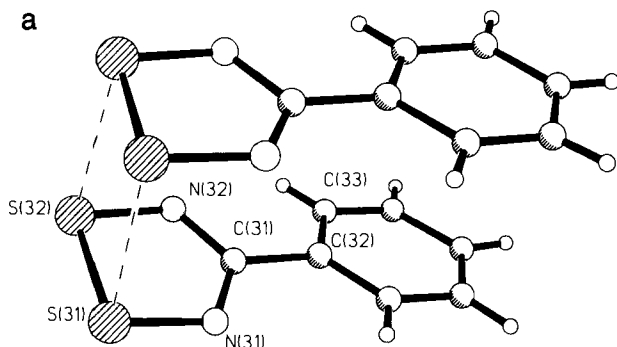


FIG. 13. Structure of (a) [Ph. $\overline{\text{CNSSN}}$]₂ and packing diagrams for (b) [*p*-MeS.C₆H₄. $\overline{\text{CNSSN}}$]₂, (c) [*p*-NC.C₆H₄. $\overline{\text{CNSSN}}$]₂, and (d) [*p*-Cl.C₆H₄. $\overline{\text{CNSSN}}$]₂.

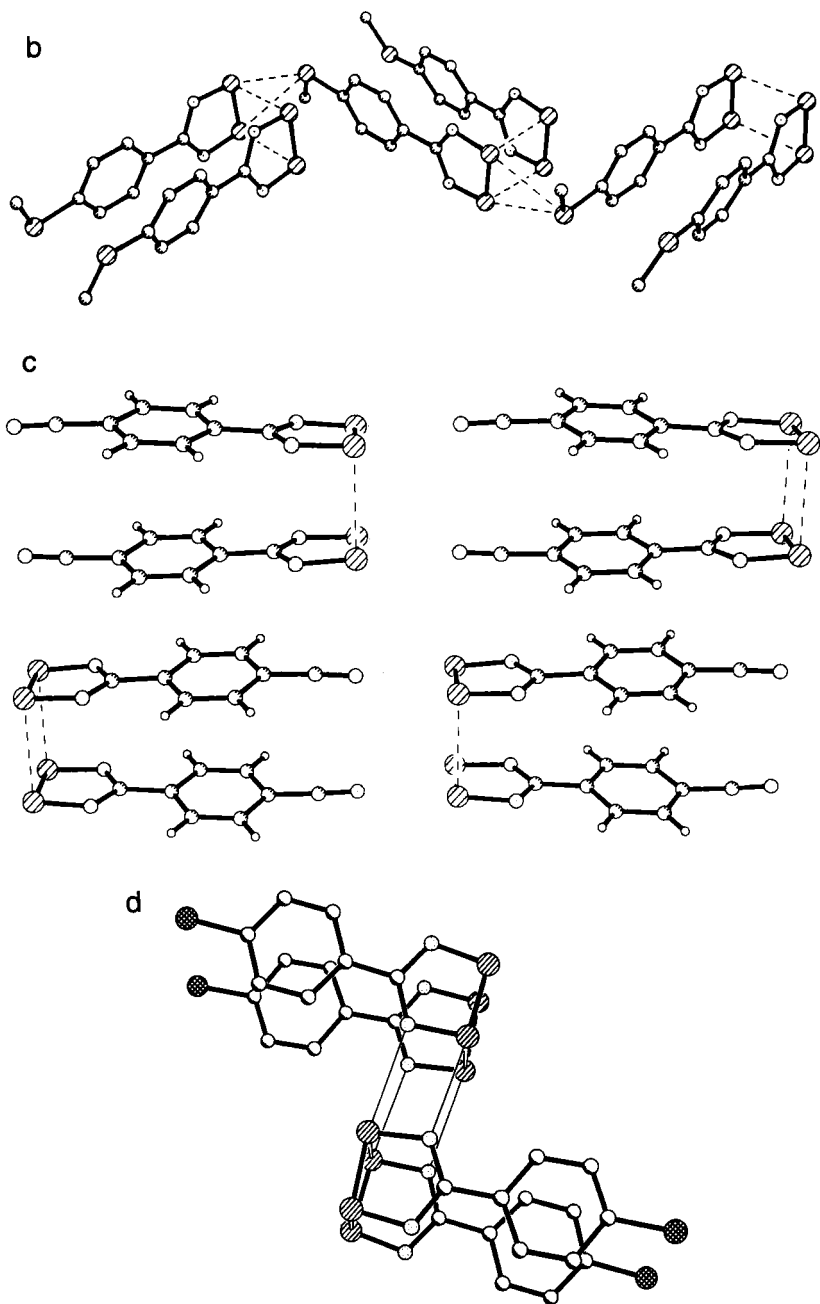


FIG. 13. (Continued)

between heterocyclic sulfur atoms and the cyano substituent; both isomers form planar sheets with in-plane cyano–disulfide interactions (Fig. 13c). In $(m\text{-NC}_6\text{H}_4\cdot\bar{\text{CNSSN}})_2$ further secondary interactions between molecular sheets leads to a structure approximating that illustrated in Figure 11, i.e., approaching the idealized situation for the formation of a conduction band. The S . . . S contacts within dimers is 3.13 Å; but unfortunately, the S . . . S distance between dimers (4.26 Å) is too long to extend the interaction beyond individual dimer pairs. Since the nitrogen lone pair in cyano-substituted derivatives lies along the C—N bond vector, the subsequent interactions are in-plane; and the change in molecular packing between chloro and cyano derivatives can be explained in terms of (i) maximizing substituent lone-pair/heterocyclic sulfur interactions and (ii) preferences of substituents for in-plane or out-of-plane interactions with the disulfide group. Similar rationalizations appear to be valid for other derivatives.

Although the structures of these radicals have been described in terms of substituent–disulfur interactions, there frequently exist a set of in-plane interactions between adjacent dithiadiazolyl rings, which can be considered to be $\text{S}^{\delta+} \cdots \text{N}^{\delta-}$ (92CJC919; 92IC1802; 93UP10; 93UP6). In the majority of cases, this can be explained in terms of an antiparallel alignment of adjacent dimer pairs (Fig. 13d) held together through two sets of S . . . N in-plane interactions. However, in the case of $(\text{MeS}\cdot\text{C}_6\text{H}_4\cdot\bar{\text{CNSSN}})_2$ only one set of S . . . N contacts is observed; the deficit of S . . . N contacts is perhaps counterbalanced by the presence of weak— $\text{SCH}_2\cdot\text{H} \cdots \text{S}$ interactions between adjacent MeS substituents.

3. *Trans-oid Configurations*

Molecular orbital calculations on dimer pairs indicate that the energy difference between cis-oid and trans-oid dimers is very small (Section VIII), and it is perhaps surprising that the majority of structures determined to date take up a cis-oid conformation. In only one case has the trans-oid configuration been observed: although $\alpha\text{-(}m\text{-NC}_6\text{H}_4\cdot\bar{\text{CNSSN}})_2$ mentioned above has a cis-oid configuration (92IC1802) there is also a second form with a trans-oid arrangement (Fig. 14). In this β -phase the cyano–dithiadiazolyl (CN . . . S) interactions are retained and the mean intradimer S . . . S separation is also similar (3.141 Å) to that observed in the α -phase. This type of structure is reminiscent of the isoelectronic **1** salts described in Section I. These **1** salts take up trans-oid configuration so as to minimize cation–cation repulsions (92MI1); however, in this case there are no such repulsions.

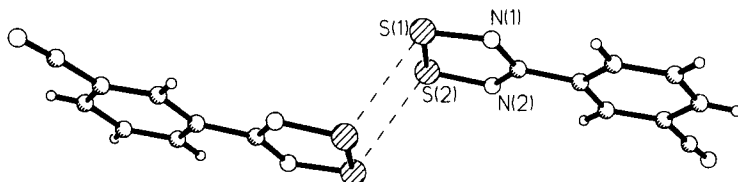


FIG. 14. Structure of β -[*m*-NC₆H₄. $\overline{\text{CNSSN}}$]₂.

This isomerism conveniently illustrates the small energy difference there is between the α and β forms (the packing efficiency is similar with calculated densities of 1.635 and 1.66 gcm⁻³ respectively).

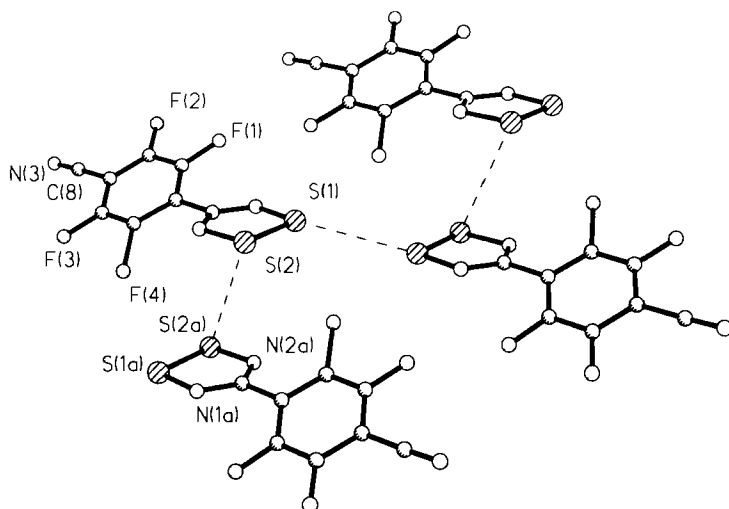
4. Monomeric Radicals

As mentioned in Section IX.A, the use of fluorinated substituents leads to an increase in spin density at the heterocyclic sulfur and slightly stronger bonding between monomers; see $d_{\text{S} \dots \text{S}}$ in [Ph $\overline{\text{CNSSN}}$]₂ and [C₆F₅. $\overline{\text{CNSSN}}$]₂ [3.109(5) Å and 3.067(2) Å, respectively]. However, a very recent X-ray structure determination has provided the first example of a dithiadiazolyl radical that does not form dimer pairs in the solid state. Although *p*-NC₆F₄. $\overline{\text{CNSSN}}$ units are packed in a *cis*-oid manner, the vertical separation between parallel rows of *p*-NC₆F₄. $\overline{\text{CNSSN}}$ (93UP10) radicals is ~4.6 Å and the packing is dominated by in-plane CN . . . S-S interactions (Fig. 15). The increased spin density at sulfur is accommodated through stronger in-plane interactions to the cyano group rather than the typical out-of-plane interactions between sulfur centers.

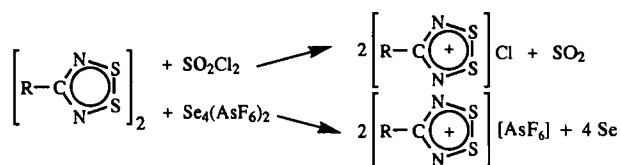
XI. Reactivity of 1,2,3,5-Dithiadiazolyl Radicals

A. OXIDATION OF DITHIADIAZOLYL RADICALS

Since **2**[•] can be prepared by reduction of the corresponding **2**⁺ salts, it is not surprising that the radicals are easily reoxidized to **2**⁺ salts. Chlorination occurs readily with SO₂Cl₂ and Cl₂ [83JCS(P1)1181], although SOCl₂, SCl₂, S₂Cl₂, and (NSCl)₃ have also been used. Bromination leads directly to the bromide, while iodination leads to a variety of polyiodides [83JCS(P1)1181]. In contrast, fluorination of **2**[•] to form [2]F has not been successfully achieved; it has been found that **2**[•] (R = Ph) reacts with N₂F₄ in liquid SO₂ to form, unexpectedly, [Ph. $\overline{\text{CNSSN}}$][SO₂F₃] (93UP5). Since

FIG. 15. The structure of $[p\text{-NC}_6\text{F}_4.\overline{\text{CNSSN}}]$.

SO_2 reacts with N_2F_4 only under photolysis conditions at 120°C (64IC1165), formation of $[\text{Ph}.\overline{\text{CNSSN}}][\text{SO}_2\text{F}_3]$ has been proposed to proceed via $[\text{Ph}\overline{\text{CNSSN}}]\text{F}_3$. This intermediate may be acyclic as found for **39**; the latter acyclic material was isolated from an attempt to fluorinate **2** ($\text{R} = \text{Cl}$) with AgF_2 (Section II.D.5).



Oxidation can also be carried out with high-oxidation-state Lewis acid halides such as SnCl_4 and with group VI polycation salts such as $\text{Se}_4(\text{AsF}_6)_2$. More interestingly, **2** ($\text{R} = \text{Ph}$) has also been shown to act as a more general dehalogenating reagent and as a radical trapping agent (see below). Oxidation with oxygen (to form an $\text{O}=\text{S}$ group) has yet to be achieved.

1. Radical Coupling Reactions

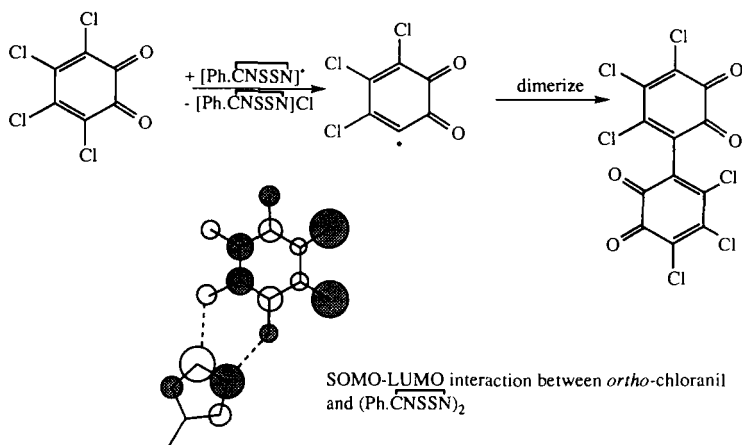
Reactions of **2** (93CC919) as a dehalogenating agent include attack at $\text{E}-\text{X}$ bonds ($\text{E} = \text{B}, \text{P}, \text{Si}$, and activated C ; $\text{X} = \text{Cl}, \text{Br}$) with formation

of new E—E bonds. For example the activated C—halogen bonds in MeCOBr and *ortho*-chloranil react with 2^{\cdot} ($R = Ph$) to form Me.CO.CO.Me and $(C_6Cl_3O_2)_2$, respectively. The nature of the reaction mechanism has not been explored, although abstraction of halogen atoms to generate an intermediate radical (E^{\cdot}) would appear likely (Scheme 6).

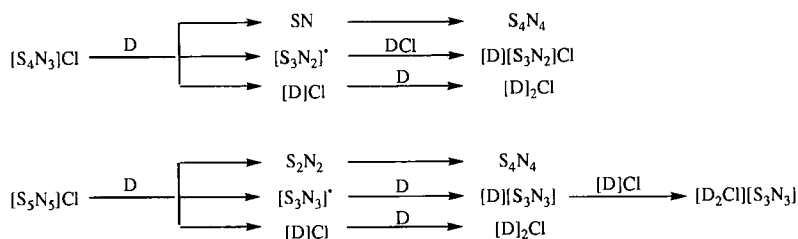
Thus radicals of type 2^{\cdot} appear to be a useful new class of coupling reagent, and modification of the substituent should allow for tailoring of reactivity. The solubility of 2^{\cdot} in a range of dry organic solvents may also make them preferable to some heterogeneous metal coupling reagents such as elemental sodium or potassium.

2. Radical-Trapping Reactions

While examining the dehalogenation properties of 2^{\cdot} , it was found that 2^{\cdot} ($R = Ph$) is capable of trapping some radical intermediates [89CC351; 90JCS(D)2793]. For instance, chemical reduction of S_5N_5Cl (**15**) normally yields S_4N_4 (**14**) and/or $(SN)_x$ [87JCS(D)915], but reaction of **15** with 2^{\cdot} yields $[2]Cl$ and $S_5N_5^{\cdot}$; the latter loses two SN^{\cdot} units to form $S_3N_3^{\cdot}$, which is then trapped by 2^{\cdot} to form $[2][S_3N_3]$ along with $[41][S_3N_3]$, and $[2]_2Cl$. Similar radical-trapping reactions occur with S_4N_3Cl to form $[2][S_3N_2]Cl$. The reactions are set out for comparison in Scheme 7, and the structures of the products are described in Section V.B–D.

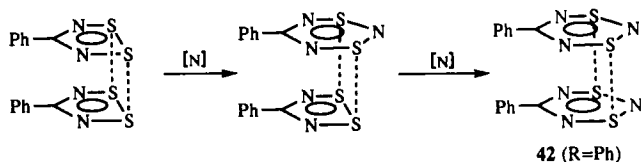


SCHEME 6. Use of $Ph.CNSSN^{\cdot}$ as coupling agent

SCHEME 7. Use of $\text{Ph}\overline{\text{CNSSN}}$ as a radical trap

B. REACTION WITH A NITROGEN PLASMA

As mentioned in Section VI.C, certain dithiadiazolylum salts react with a cool dc nitrogen plasma to form dithiatriazines. Such ring-expansion reactions were initially observed for the radicals $2'$ in the solid state [87CC63; 89JCS(D)1705], particularly where $R = \text{Ph}$ and $p\text{-Cl.C}_6\text{H}_4$. Since the reaction occurs only in the solid state, a mechanism was proposed involving transport of highly reactive N atoms (the main product of a nitrogen plasma is the ground-state N atom, ^4S , formed by the dissociation of N_2 (57PC902)). The nitrogenation of $(2)_2$ ($R = \text{Ph}$, $p\text{-Cl.C}_6\text{H}_4$) readily occurred to give **42**, but $(\text{Me}.\overline{\text{CNSSN}})_2$ gave only a polymeric tar. The structures of $(\text{Ph}.\overline{\text{CNSSN}})_2$ and $(\text{Me}.\overline{\text{CNSSN}})_2$ are distinctly different (see Sections X.B.1 and 2); and of the two, only $(\text{Ph}.\overline{\text{CNSSN}})_2$ has channels large enough to allow rapid transport of N atoms. Significantly $(p\text{-Cl.C}_6\text{H}_4.\overline{\text{CNSSN}})_2$ also undergoes a nitrogen-insertion reaction, but $(\text{Pr}.\overline{\text{CNSSN}})_2$ and $(\text{Bu}.\overline{\text{CNSSN}})_2$ do not. Thus it appears that some, perhaps most, aryl derivatives possess tunnels sufficiently large to permit the rapid transport of $\text{N}[^4\text{S}]$, whereas the alkyl derivatives do not. Since several salts, including $[\text{Ph}.\overline{\text{CNSSN}}][\text{S}_3\text{N}_3]$, also undergo plasma nitrogenation to give **42**, one supposes that their structures similarly facilitate nitrogen transport.

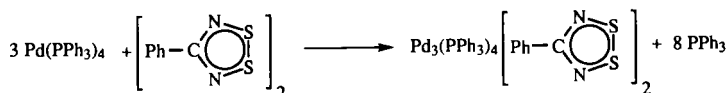


C. REACTION WITH TRANSITION METAL COMPLEXES

In examining the chemistry of $(\text{Ph}.\overline{\text{CNSSN}})_2$ as a typical example of the $2'$ family of radicals, it was found that it readily formed complexes

with transition metals in which the heterocyclic S—S bond expands, leading to two μ_2 bridging sulfur atoms. For example, $(\text{PhCNSSN})_2$ reacts with $(\text{CpNiCO})_2$ to give paramagnetic $\text{Cp}_2\text{Ni}_2[\text{PhCNSSN}]$ [91JCS(D)1105]. The iron complex formed from $(\text{PhCNSSN})_2$ and $\text{Fe}_2(\text{CO})_9$ is readily hydrolyzed to give $\text{Fe}_2(\text{CO})_6[\text{PhCN}(\text{H})\text{SSN}]$ (941Cip). The structures of three dithiadiazolyl complexes are shown in Figure 16.

Many other metal carbonyls also gave insoluble, involatile products. Higher yields of more crystalline complexes with one or more metal atoms were achieved when using cyclopentadienyl or phosphine-donor ligands. For example, $\text{Pt}(\text{PPh}_3)_4$ reacted with $[\text{PhCNSSN}]_2$ to form $\text{Pt}_2[\text{PPh}_3]_2[\text{PhCNSSN}]$ in 75% yield, which on thermolysis formed $\text{Pt}_3[\text{PPh}_3]_4[\text{PhCNSSN}]_2$. Reaction of $(\text{PhCNSSN})_2$ with $\text{Pd}(\text{PPh}_3)_4$ yielded only the analogous complex, $\text{Pd}_3[\text{PPh}_3]_4[\text{PhCNSSN}]_2$ (93UP11). This trimetallic species (Fig 16c) possesses a central Pd atom bonded via two bridging (PhCNSSN) ligands to two terminal $\text{Pd}(\text{PPh}_3)_2$ units.



Pure samples of both $\text{Pt}_3[\text{PhCNSSN}]_2[\text{PPh}_3]_4$ and its Pd analog are diamagnetic, indicating pairing of the radical electrons, presumably through a delocalized molecular orbital based on the $\text{M}_3\text{S}_4\text{P}_4$ framework. Of the monometallic species studied, $\text{Pt}[\text{PPh}_3]_2[\text{PhCNSSN}]$ exhibits Curie-Weiss behavior to below 20K, typical of an $S = \frac{1}{2}$ paramagnet (93UP11). ESR studies (94CC1779) show that the unpaired electron becomes delocalized onto the metal framework. Samples of some of these complexes have also shown superparamagnetic behavior, which has been associated with radical impurities in the lattice. Some of these materials have been shown, by ESR spectroscopy, to contain traces of **2'**, although the superparamagnetic response may also be attributable in certain cases to traces of elemental metal formed through decomposition of the complex or carbonyl starting material. Such superparamagnetism has also been observed in salts of **3**⁺ (Section XIV.C) and charge-transfer salts of **2**⁺ (Section IV.D), which have been shown by ESR to contain trace quantities of the radicals **1** and **2**, respectively.

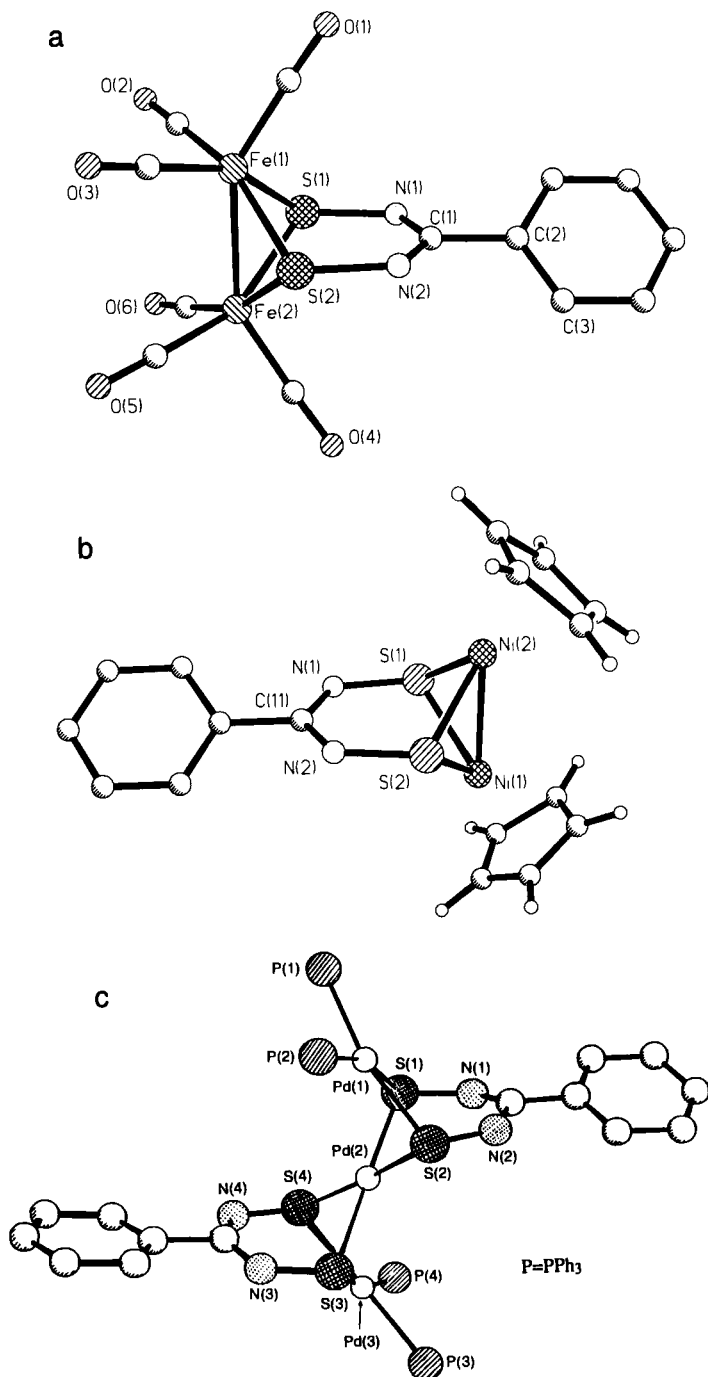


FIG. 16. Crystal structures of (a) $\text{Fe}_2(\text{CO})_6[\text{Ph}.\overline{\text{CNSSNH}}]$, (b) $\text{Cp}_2\text{Ni}_2[\text{Ph}.\overline{\text{CNSSN}}]$, and (c) $\text{Pd}_3[\text{PPh}_3]_4[\text{Ph}.\overline{\text{CNSSN}}]_2$.

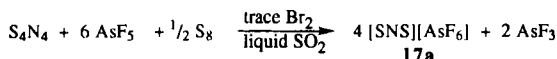
XII. Preparation of Mono-1,3,2,4-Dithiadiazolylium Salts

A. [SNS][AsF₆] AS A BUILDING BLOCK IN SULFUR–NITROGEN CHEMISTRY

The dithianitronium cation, as the hexafluoroarsenate(V) salt [SNS]-[AsF₆] **17a** (and to a lesser extent [SNS][SbCl₆]), is a highly versatile reagent for the synthesis of sulfur–nitrogen heterocycles (94ACR101). Its high reactivity is frequently coupled with good yields (often quantitative by nmr) and also regio- and stereoselectivity. A brief summary of its preparation and reactivity is given below.

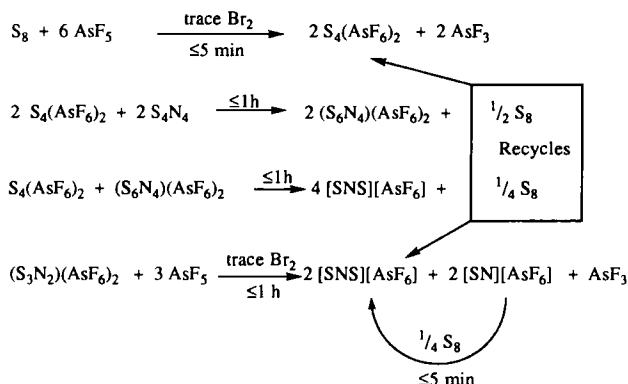
1. Preparation of [SNS][AsF₆]

This salt is most commonly prepared by oxidation of sulfur and S₄N₄ **14** with AsF₅ **44** in liquid SO₂ in the presence of a catalytic quantity of bromine (82IC1679). However, this route is potentially hazardous in inexperienced hands: S₄N₄ is explosive and AsF₅ is a highly toxic gas. The whole reaction is carried out under pressure (~3–4 bar).

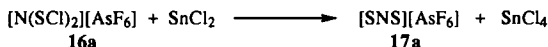


A detailed mechanistic study [92JCS(D)1343] has shown that the primary step in the reaction sequence is oxidation of S₈ to give S₄(AsF₆)₂ **45**, which then reacts with S₄N₄ to form [S₃N₂]₂[AsF₆]₂ **1**[AsF₆] (Scheme 8). Compound **1** is further oxidized to form **17a** and [SN][AsF₆] **46**, the latter reacting with the sulfur to give **17a**.

Other preparations have also been reported [82IC1679; 86IC4451; 87JCS(D)1565], and more recently, directed syntheses from less haz-



SCHEME 8. Preparation of [SNS][AsF₆] from S₄N₄, S and AsF₅

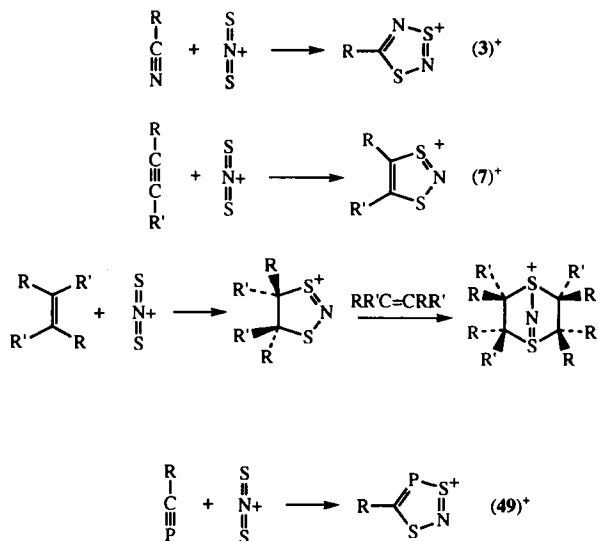


ardous reagents have been described [90JCS(D)1517; 92JCS(D)1343; 92JCS(D)3097]. Of these, potentially the most useful is the dechlorination of $[\text{N}(\text{SnCl}_2)_2]^+$ salts **16** with SnCl_2 . This general route facilitates the preparation of a variety of salts of **17** and has allowed for a comparison of their reactivities [92JCS(D)3097].

Other salts of **16** can be prepared in high yields through several routes [79INCL175; 80ZN(B)657; 83JCS(D)1961; 92JCS(D)3097] from nonhazardous reagents, most involving **11**.

2. Reaction of $[\text{SNS}][\text{AsF}_6]$ with Alkynes

$[\text{SNS}][\text{AsF}_6]$ **17a** reacts as a 4π -diene in a variety of cycloaddition reactions with 2π -dienophiles, such as $\text{R}-\text{C}\equiv\text{C}-\text{R}'$ [83CC807; 85JCS(D)1405; 87CC66; 91IC3342; 92MRC666], to form **7**⁺ (Scheme 9). Alkynes, with a wide variety of substituents, including CF_3 , H, Me_3Si , Me, CN, and Ar, have been examined. In the case of simple alkyl derivatives, white crystalline solids are isolated, but aryl derivatives often contain small amounts of highly colored impurity which is not so readily removed (91IC3342). Yields, as indicated by nmr are frequently quantitative, and recovered yields are normally in excess of 80%. The reactions



SCHEME 9. Reaction of $[\text{SNS}][\text{AsF}_6]$ with organic reagents

are first-order in both reactants—consistent with a cycloaddition process. The rates of cycloaddition are approximately proportional to the negative ionization potential of the triple bond (91IC3342); this is consistent with the reverse electron demand process outlined later (Section XII.B).

3. Reaction of $[SNS][AsF_6]$ with Alkenes

The cycloaddition chemistry of **17a** to alkenes $R_2C=CR_2$ **47** is not nearly as extensive; reactions occur only with activated alkenes such as $H_2C=CH_2$ and $E-MeHC=CHMe$ (86CC966) (Scheme 9). Both 1 : 1 and 2 : 1 addition products have been isolated. Reaction occurs only with electron-rich alkenes, since these have sufficiently high energy HOMOs to allow electron drift from **47** to the LUMO of **17**.

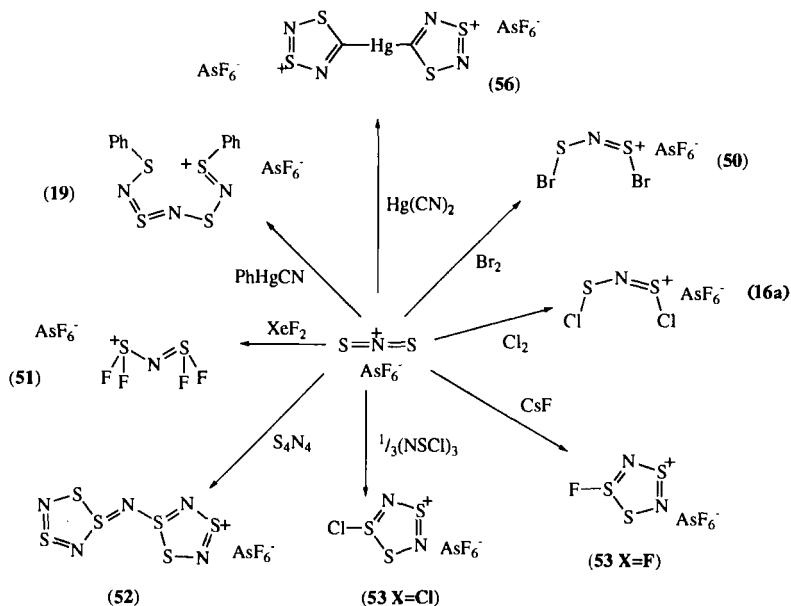
4. Reaction of $[SNS][AsF_6]$ with Phosphaalkynes

The possibility that **17a** may react with phosphaalkynes $RC\equiv P$ **48** to form C/S/N/P heterocycles **49** was first proposed in 1991 (91IC3342) and has been reported recently (92MRC666) for the *t*Bu derivative (see Scheme 9).

5. Reaction of $[SNS][AsF_6]$ with Inorganic Reagents

Compound **17a** can be oxidized by Cl_2 , Br_2 , and XeF_2 [83JCS(D)1961] to form **16a**, $[N(SBr)_2][AsF_6]$ **50**, and $[N(SF_2)_2][AsF_6]$ **51**, respectively (Scheme 10). Of these materials **16a** also undergoes cycloaddition chemistry, although its reactivity is significantly less than that of **17a** (90CJC852). Compound **17a** also reacts with a variety of unsaturated inorganic systems, such as S_4N_4 [84JCS(D)211] and the $S\equiv N$ bond in $[N\equiv S^+]$ or $N\equiv S-X$ ($X = Cl, F$) [88IC2749; 91IC3342; 92JCS(D)1343].

Recent studies (92TH1; 93UP1; 94CC29) of the reactions of metal cyanides with **17a** have shown that $Ph.Hg.CN$ **54** reacts with **17a** to form, unexpectedly a cationic S_4N_3 chain terminated by phenyl groups, $[Ph.SNSNSNS.Ph][AsF_6]$; see the chloride salt **19** in Scheme 3. In contrast, $Hg(CN)_2$ **55** reacts in a similar manner to organic analogs RCN to form $[Hg(CNSNS)_2][AsF_6]_2$ **56**. The chemistry of **56** is likely to be diverse since preliminary reactions (see Section XII.E) show that it can be used as a transfer agent for the $-CNSNS^+$ functional group (94CC29).

SCHEME 10. Reaction of $[\text{SNS}][\text{AsF}_6]$ with inorganic reagentsB. REACTION OF NITRILES WITH $[\text{SNS}][\text{AsF}_6]$

The reactions of **17a** with nitriles have been examined extensively and have been shown (by nmr), in many cases, to proceed quantitatively in liquid SO_2 . Yields are commonly in excess of 80%. A summary of all published reactions of this type is given in Table IX. In the majority of cases, reaction proceeds smoothly at room temperature over 1–24 h.

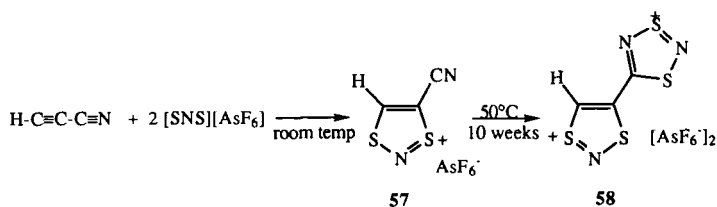
Kinetic studies by Passmore and co-workers (91IC3342) have shown that the cycloaddition reactions of **17** with alkynes, nitriles, and alkenes may best be described as Sustmann type III (84MI1); the reaction can be thought of as a reverse-electron-demand cycloaddition process; i.e., the major interaction is electron donation from the dienophile HOMO to the LUMO of **17** (80MI1; 86CC966; 91IC3342). The frontier orbitals of RCN and **17** are shown in Figure 17. Since the π -MOs of **17** are of such low energy, cycloaddition reactions are observed for even the most electrophilic nitriles (91IC3342). Modification of the nitrile substituent R may alter the HOMO–LUMO energy gap and consequently change the relative reactivities of nitriles to **17**. Thus $\text{Me}_2\text{N.CN}$ reacts 50 times faster than $t\text{Bu.CN}$ and 100 times quicker than MeCN (91IC3342). Such variation in reactivity is not limited to nitriles, but applies also to alkynes; and in

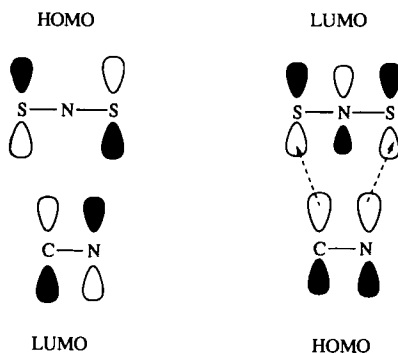
TABLE IX
PREPARATION OF 1,3,2,4-DITHIA DIAZOLYLIUM SALTS FROM [SNS][AsF₆]
AND NITRILES

Nitrile substituent	Yield	Reference
Me	100, ^a 97	83CC807; 85JCS(D)1405; 88CJC1299; 91IC3342
CF ₃	100, ^a 89	86CC140
<i>t</i> Bu	89	87CC69; 91IC3342; 92MRC666
I	100, ^a 89	86CC140; 91IC3342
H	100, ^a 93	91IC3342
Me ₂ N	100 ^a	91IC3342
Ph	100, ^a 95, 90	91IC3342; 93JCS(D)967; 92JCS(D)3097
<i>p</i> -O ₂ N.C ₆ H ₄	100, ^a 88	91IC3342; 93JCS(D)967
3,5-(O ₂ N) ₂ C ₆ H ₃	100 ^a	91IC3342
2,5-(Me) ₂ C ₆ H ₃	100 ^a	91IC3342
<i>p</i> -CF ₃ .C ₆ H ₄	92	93JCS(D)967
<i>p</i> -Br.C ₆ H ₄	80	93JCS(D)967
<i>p</i> -Cl.C ₆ H ₄	95	93JCS(D)967
<i>p</i> -F.C ₆ H ₄	96	93JCS(D)967
<i>p</i> -MeS.C ₆ H ₄	83	93JCS(D)967
<i>p</i> -Me.C ₆ H ₄	72	93JCS(D)967
<i>p</i> -MeO.C ₆ H ₄	65	93JCS(D)967
C ₆ F ₅	94	92JCS(D)3097
HCSNSC	100 ^{a,b}	91CC369; 91IC3342
<i>m</i> -F.C ₆ H ₄	75	93UP14
<i>o</i> -F ₃ C.C ₆ H ₄	72	93UP14
<i>o</i> -F.C ₆ H ₄	77	93UP14
<i>o</i> -H ₃ C.C ₆ H ₄	94	92TH1
<i>o</i> -Cl.C ₆ H ₄	— ^c	93UP14
<i>o</i> -Br.C ₆ H ₄	61	93UP14

^a Quantitative by nmr.^b Only after 10 weeks at 50°C in liquid SO₂.^c Unspecified.

the case of cycloaddition of **17** with H—C≡C—C≡N reaction occurs preferentially at the alkyne bond, and only **57** is isolated (91CC369; 91IC3342); at ambient temperature. More forcing conditions are required to form the 2 : 1 product **58**.

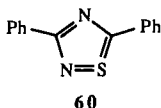


FIG. 17. Frontier orbitals of a nitrile and SNS^+ .

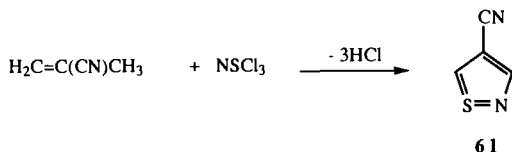
Mechanistically, the cycloaddition process would appear to be highly asynchronous (91IC3342), and MO calculations indicate that a transition state involving $[\text{RC}\equiv\text{N}^{\delta-} \cdots ^+\text{SNS}]$ interactions is involved, followed by cyclization. Although there are several other routes to 1,3,2,4-dithiadiazolylium (3^+) salts (described below), cycloaddition of $[\text{SNS}]$ $[\text{AsF}_6]$ with the parent nitrile would appear to constitute the only general quantitative route available.

C. FROM THIOACETAMIDES AND NSCl_3

Chivers and co-workers have examined the use of $(\text{NSCl})_3/\text{SO}_2\text{Cl}_2$ as an in situ source of NSCl_3 **59** (87CC1889; 90CJC650), and found that “ NSCl_3 ” reacted with thioamides to form $[\text{RCNSNS}]\text{Cl}$ via a condensation reaction; thioacetamide forms $[\text{MeCNSNS}]\text{Cl}$ in high yield and thio-benzamide forms $[\text{PhCNSNS}]\text{Cl}$ in 42% yield. However, it was found that the latter was contaminated with appreciable quantities of 3,5-diphenyl-1,2,4-thiadiazole **60** (51%). Consequently, further work is required to ascertain the generality of this route to 3^+ salts.

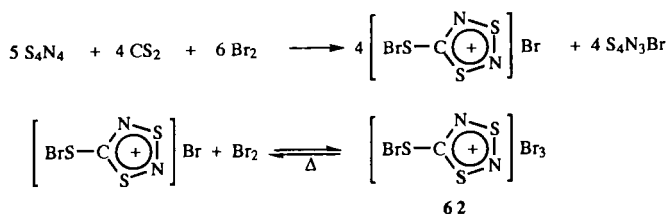


Nevertheless, this reagent appears to be a useful synthetic tool for the preparation of S/N heterocycles; for instance, it also reacts with methacrylonitrile via condensation (90CJC650) to form **61**.



D. REACTION OF S_4N_4 WITH Br_2 IN CS_2

Wolmershäuser and co-workers (79IC383; 82CB1126) found that reaction of S_4N_4 with bromine in CS_2 at ambient temperature led to a mixture of products including $[\text{BrS}.\overline{\text{CNSNS}}]\text{Br}$ and $[\text{BrS}.\overline{\text{CNSNS}}]\text{Br}_3$ **62**. The two salts can be interconverted via bromination or warming in vacuo.

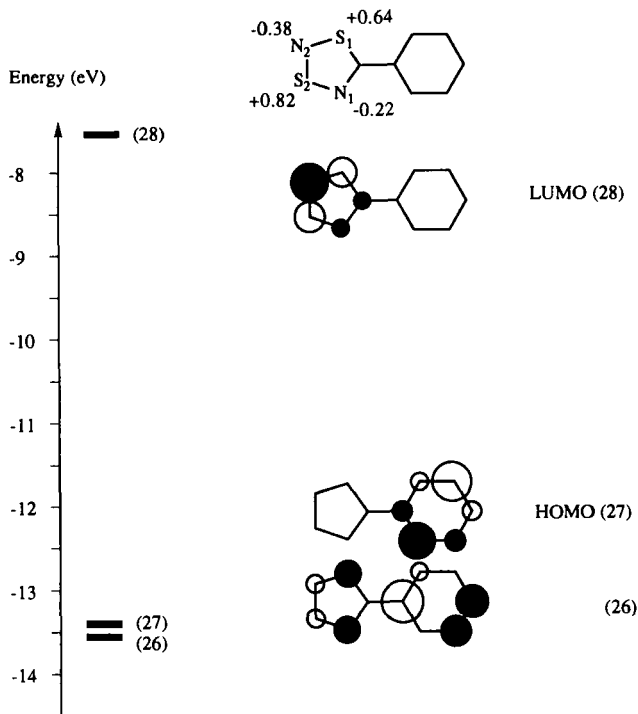


E. BY RING TRANSFER

$[\text{Hg}(\overline{\text{CNSNS}})_2][\text{AsF}_6]_2$ **56** reacts with bromine and iodine to produce $\text{Hg}_n\text{X}_2(n = 1, 2)$ and $[\text{X}.\overline{\text{CNSNS}}][\text{AsF}_6]$ ($\text{X} = \text{Br}$ or I) (94CC29) (see Section XXIII.A).

XIII. Theoretical Studies of 1,3,2,4-Dithiadiazolylium Salts

Molecular orbital calculations (PM3 and INDO) for 1,3,2,4-dithiadiazolylium cations (Fig. 18) show that both the sulfur atoms are positively charged, with $\text{S}_{(2)}$ (farthest from the substituent) possessing the higher charge [85JCS(D)1405; 92JCS(D)3097]. Consequently, cation-anion interactions are largely expected to involve the $\text{S}^{\delta+}$ centers with a preference for $\text{S}_{(2)}^{\delta+}$. This is seen in $[\text{Ph}\overline{\text{CNSNS}}][\text{AsF}_6]$ [92JCS(D)3097]. For softer anions, some degree of covalency, especially at $\text{S}_{(2)}$, can be anticipated. Unfortunately, there are no structure determinations as yet on any halide [3]X. INDO calculations on these salts provide poor agreement between calculated and experimental bond lengths, although bond angle correlations are better [85JCS(D)1405]. In comparison, INDO calculations on **3'**

FIG. 18. Molecular orbital diagram for $[\text{Ph}.\overline{\text{CNSNS}}]^+$.

provide excellent esr predictions (Section XIX) and improved structural correlations [85JCS(D)1405].

A statistical analysis of differences between empirical and calculated heats of formation for many hundreds of compounds (89MI2) shows that for most elements (including H, C, N, F, and S) the PM3 method is considerably more reliable than MNDO or AMI. Consequently, caution is necessary in interpreting data from MO calculations, particularly from the MNDO and simpler INDO methods.

XIV. Physical Properties of 1,3,2,4-Dithiadiazolylum Salts

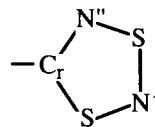
A. MULTINUCLEAR NUCLEAR MAGNETIC RESONANCE SPECTRA

The nmr data available for 1,3,2,4-dithiadiazolylum salts are compiled in Table X. Studies by Passmore and co-workers have shown the ring-

TABLE X
MULTINUCLEAR NMR DATA FOR 1,3,2,4-DITHIADIAZOLYLIUM SALTS^a

Salt	Solvent	¹ H	¹⁹ F	¹³ C	¹⁴ N	Reference
[Ph. $\overline{\text{CNSNS}}$][SbCl ₆]	CD ₃ CN	8.97, 8.61, 8.45				92JCS(D)3097
[Ph. $\overline{\text{CNSNS}}$]Cl	acetone				– 277	90CJC650
[C ₆ F ₅ . $\overline{\text{CNSNS}}$][SbCl ₆]	CD ₃ CN		– 132.2, – 140.2, 159.7			92JCS(D)3097
[H. $\overline{\text{CNSNS}}$][AsF ₆]	SO ₂	10.6	– 57 (q, AsF ₆ [–])	144 (C _r)	– 16 (N'), + 25 (N'')	91IC3342
[I. $\overline{\text{CNSNS}}$][AsF ₆]	SO ₂		– 57 (q, AsF ₆ [–])	146 (C _r)	– 9 (N'), + 37 (N'')	91IC3342
[Me. $\overline{\text{CNSNS}}$][AsF ₆]	SO ₂	4.82 (or 1.9)	– 57 (q, AsF ₆ [–])	208 (C _r), 18 (Me)	– 27 (N'), + 126 (N'')	91IC3342
						85JCS(D)1405
[Me. $\overline{\text{CNSNS}}$]Cl	acetone	1.22			– 271, – 286	90CJC650
[<i>t</i> Bu. $\overline{\text{CNSNS}}$][AsF ₆]	SO ₂	1.9	– 57 (q, AsF ₆ [–])	223 (C _r), 42 ($\overline{\text{CMe}_3}$), 30 (Me)	– 28 (N'), + 28 (N'')	91IC3342
[CF ₃ . $\overline{\text{CNSNS}}$][AsF ₆]	SO ₂		– 58 (CF ₃), – 57 (q, AsF ₆ [–])	118 (CF ₃ , J _{CF} = 280 Hz) 193 (C _r , J _{CF} = 48 Hz)	– 11 (N'), + 32 (N'')	91IC3342
[Me ₂ N. $\overline{\text{CNSNS}}$][AsF ₆]	SO ₂	3.5, 3.6	– 57 (q, AsF ₆ [–])		– 17 (N'), – 101 (N'') – 266 ($\overline{\text{NMe}_2}$)	91IC3342
Chemical shifts referenced to:						
		Me ₄ Si	CFCl ₃	Me ₄ Si	Me.NO ₂	

^a Heterocyclic-ring assignments are given in accordance with the following diagram:



carbon resonance (C_r) to be typically in the region of 144–223 ppm or, more specifically, 90 ± 10 ppm higher than the corresponding nitrile starting material (91IC3342). Although ^{13}C nmr data are available for only one derivative of the isomeric 2^+ heterocycle, the two isomers would appear to have similar chemical shifts. ^{14}N nmr data show two resonances attributable to the two chemically distinct N atoms, N' and N'' : the N' (–28 to –16 ppm) resonances tend to be broader and occur over a wider chemical shift range than for N'' , reflecting a more pronounced substituent (R) effect at the N' nucleus (91IC3342). Such an effect also appears to be observed in the esr spectra for the reduced analogs (Section XVIII.A). Surprisingly, only one resonance was observed for $[\text{Ph}.\bar{\text{C}}\text{NSNS}]\text{Cl}$, although the different solvent (acetone instead of SO_2) certainly indicates a strong solvent dependency (cf. $[\text{Me}\bar{\text{C}}\text{NSNS}]\text{Cl}$ and $[\text{Me}\bar{\text{C}}\text{NSNS}][\text{AsF}_6]$ (90CJC650)). Unsurprisingly, substituent resonances also shift to lower field, in accordance with an increase in net positive charge with respect to the parent nitrile.

B. ELECTROCHEMICAL STUDIES

A recent study [93JCS(D)967] of aryl-1,3,2,4-dithiadiazolylum salts has shown that they typically show a half-wave reduction potential in the region $+0.29 \leq E_{1/2} \leq +0.4$ V (with reference to the standard calomel electrode). As found for the 1,2,3,5-isomers, these salts show a Hammett relationship between $E_{1/2}$ and the σ value for the para substituent on the aryl group. The greater reaction constant ρ , for the $3^+/3'$ redox system, compared with $2^+/2'$, is in agreement with MO calculations—which indicate some unpaired spin density on the heterocyclic carbon, allowing delocalization onto the aryl substituent. (The nodal plane associated with $2'$ prohibits, to a first-order approximation, delocalization with the aryl functionality.)

Because of isomerization of $3'$ to the more stable $2'$ (Sections XXI.A.1 and XXIII.G.2,3), cyclic voltammograms of 3^+ salts tend to show weak electroactive peaks due to the redox system $2^+/2'$. Such effects are most prominent when using slow scan rates with radicals that rearrange significantly at ambient temperatures.

C. 1,3,2,4-DITHIADIAZOLYLUM SALTS AS HOST LATTICES FOR S_3N_2^{+} RADICALS

Reaction of MeCN with a slight excess of $[\text{SNS}][\text{AsF}_6]$ was found to provide $[3][\text{AsF}_6]$ (R = Me) in high yield. However, this material was found to be contaminated with $[\text{S}_3\text{N}_2][\text{AsF}_6]$, $[1][\text{AsF}_6]$ (presumably

formed in small quantities by a minor side reaction, e.g., disproportionation of $[\text{SNS}]^+$ to give $[\text{S}_3\text{N}_2]^{+ \cdot}$ and polysulfur cations $[\text{S}_x]^{2+}$). ESR studies on single crystals of $[\mathbf{3}][\text{AsF}_6]$ ($\text{R} = \text{Me}$) showed the radical cation **1** substitutes for the host cation $\mathbf{3}^+$ in the lattice, leading to doping of the diamagnetic material with variable quantities of well oriented paramagnetic centers. Indeed, these authors have found that some samples of other derivatives of $[\mathbf{3}][\text{AsF}_6]$ also show traces of radical impurity leading to spontaneous magnetization at room temperature (93UP9). Such superparamagnetism² has also been observed in charge-transfer salts, such as $[\text{PhCNSSN}][\text{S}_3\text{N}_3]$ (shown to contain $[\text{PhCNSSN}]^{\cdot}$ impurities; Section IV.D) and the metal complexes (e.g., $\text{Cp}_2\text{Ni}_2[\text{PhCNSSN}]$), which sometimes contain impurities of $[\text{PhCNSSN}]^{\cdot}$ (Section XI.C). Whether such a magnetic response can be unequivocally attributed to sulfur–nitrogen free radicals of type **1** and/or **2**[·] is doubtful at the present time: trace quantities of ferromagnetic impurity would lead to a similar response.

XV. X-Ray Diffraction Studies of 1,3,2,4-Dithiadiazolylium Salts

Three structures of mono-1,3,2,4-dithiadiazolylium salts have been reported: the first, $[\text{BrS.CNSNS}][\text{Br}_3]$ **62** in 1982 (Fig. 19a) (82CB1126), followed by $[\text{MeCNSNS}][\text{AsF}_6]$ (Fig. 19b) [83CC807; 85JCS(D)1405], and more recently by $[\text{PhCNSNS}][\text{AsF}_6]$ [92JCS(D)3097].

Although all three structures have similar dimensions, some heterocyclic bond lengths appear slightly anomalous (Table XI), particularly $d_{\text{N}'\text{S}'}$ (mean value 1.64 ± 0.03 Å): the long $\text{N}'\text{—S}'$ bond in $[\text{BrS.CNSNS}][\text{Br}_3]$ may be attributed to secondary cation–anions ($\text{S}' \cdots \text{Br}_3$) interactions, leading to a weakening of the corresponding $\text{S}'\text{—N}'$ bond. Cation–anion interactions, present in the hexafluoroarsenate(V) salts, have also been studied. Both $[\text{MeCNSNS}][\text{AsF}_6]$ and $[\text{PhCNSNS}][\text{AsF}_6]$ show $\text{S} \cdots \text{F}$ and $\text{H} \cdots \text{F}$ interactions, the strongest of these being those associated with $\text{S}_{(2)}$, which bears the larger positive charge (Section XIII) [92JCS(D)3097]—but these are significantly weaker than the interactions in **62**. There are no secondary interactions between the anion and heterocyclic nitrogen atoms, indicating that both nitrogen atoms possess partial negative charges, leading to $\text{N}^{\delta-} \cdots \text{AsF}_6^-$ repulsion.

² Superparamagnetism arises through the spontaneous alignment of unpaired electrons with an applied magnetic field, and is frequently observed for ferro fluids. In such materials there must be a long-distance exchange pathway between submicron domains of paramagnetic particles. Such materials have an extremely low coercivity and tend not to exhibit hysteresis (89MI1).

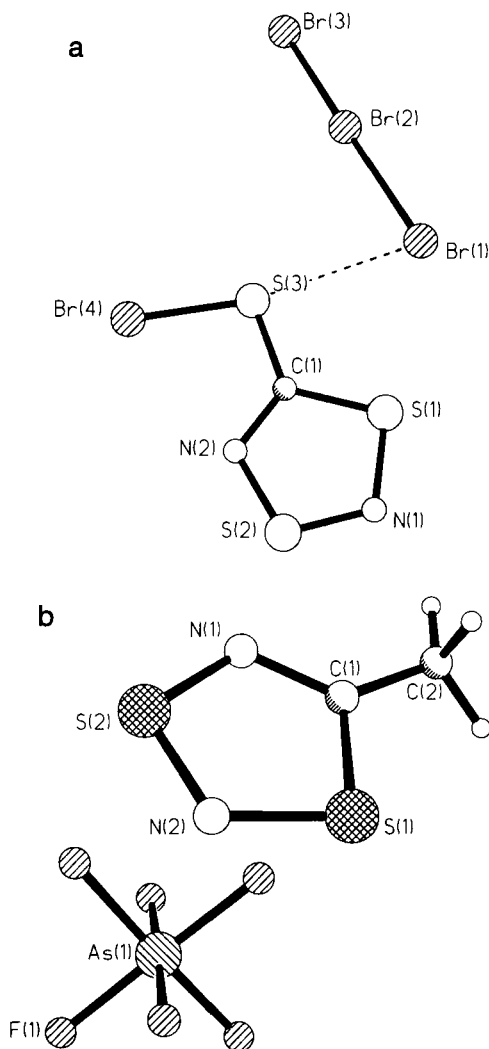


FIG. 19. Crystal structures of (a) $[\text{BrS.CNSNS}]\text{Br}_3$ and (b) $[\text{Me.CNSNS}][\text{AsF}_6]$.

XVI. Reactivity of 1,3,2,4-Dithiadiazolylium Salts

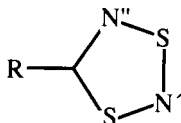
A. 1,3,2,4-DITHIADIAZOLYLIUM SALTS AS CATIONIC INITIATORS FOR THE POLYMERIZATION OF THF

A variety of cationic sulfur–nitrogen species, e.g., $[\text{SN}][\text{AsF}_6]$ (46), $[\text{SNS}][\text{AsF}_6]$ (17a), and $[\text{S}_3\text{N}_2][\text{AsF}_6]$ ([1][AsF_6]), have been shown to act

TABLE XI
HETEROCYCLIC BOND DISTANCES AND ANGLES FOR 1,3,2,4-DITHIADIAZOLIUM SALTS

	Bond Length (Å)					Reference
	C—N''	N''—S''	S''—N'	N'—S'	S'—C	
[BrS. $\overline{\text{CNSNS}}$]Br ₃	1.37(2)	1.60(2)	1.56(2)	1.67(1)	1.76(1)	82CB1126
[Me. $\overline{\text{CNSNS}}$][AsF ₆]	1.32(3)	1.57(2)	1.59(2)	1.63(2)	1.77(2)	83CC807
						85JCS(D)1405
[Ph. $\overline{\text{CNSNS}}$][AsF ₆]	1.332(9)	1.576(7)	1.563(8)	1.596(8)	1.735(8)	92JCS(D)3097
	Bond Angle (°)					Reference
	S''-C-N''	C-N''-S''	N''-S''-N'	S''-N'-S'	N'-S'-C	
[BrS. $\overline{\text{CNSNS}}$]Br ₃	114(1)	112(1)	106.0(8)	112.0(9)	96.3(7)	82CB1126
[Me. $\overline{\text{CNSNS}}$][AsF ₆]	111(2)	116(2)	104.6(9)	110.4(2)	98.4(9)	83CC807
						85JCS(D)1405
[Ph. $\overline{\text{CNSNS}}$][AsF ₆]	111.8(5)	114.4(5)	103.3(4)	112.9(4)	97.5(4)	92JCS(D)3097

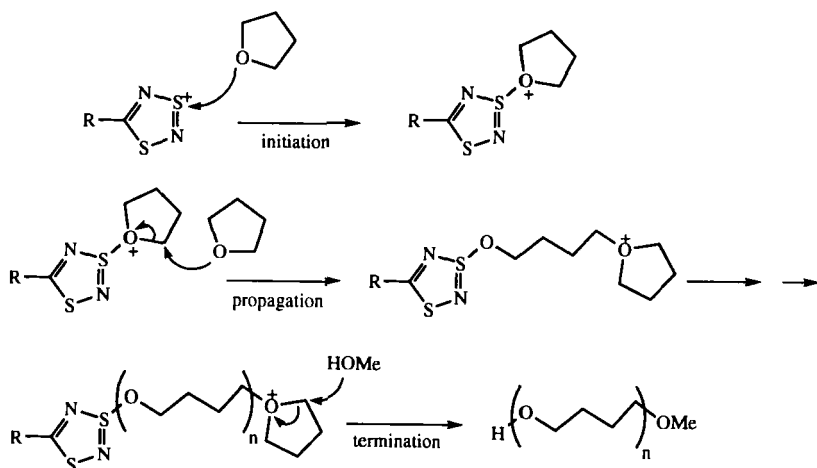
^a Heterocyclic-ring assignments are given in accordance with the following diagram:



as cationic initiators for the polymerization of THF **63** (85MRC828). However, such mechanisms appear complex; the polymers so formed tend to be an intense brown color, and esr spectra show the presence of the radical cation **1**. In contrast, the gels formed from [3][AsF₆] (R = Ph) and THF (over a period of several hours at room temperature) are clear and esr-inactive, indicating a cationic ring-opening polymerization (CROP) mechanism [92JPS(A)2653]. The reaction has been proposed to proceed via coordination of THF to the most positive sulfur (Section XIII), followed by subsequent attack of a second THF molecule (see Scheme 11). The polymers formed in this way were typically of high molecular weight (190,000–200,000 g mol⁻¹) and low polydispersity (1.61–1.96). The isomeric salts [2][AsF₆], which do not possess such a high positive charge at sulfur (~+0.5; see Section III), do not polymerize **63** in the same manner.

B. REDUCTION OF 1,3,2,4-DITHIADIAZOLYLIUM SALTS

Reduction of 3⁺ cations (as the AsF₆⁻ salt) with reducing agents, such as silver powder [83CC807; 85JCS(D)1405], Ph₃Sb/[Me₄N]Cl (86CC140; 87CC69), or Na₂S₂O₄ [85JCS(D)1405], leads to the formation of the corre-

SCHEME 11. Mechanism of polymerization of THF by $[\text{Ph}.\bar{\text{C}}\text{NSN}\bar{\text{S}}][\text{AsF}_6]$

spending **3'** free radical (Section XVII). In the majority of cases, where the free radical is soluble in organic solvents and/or SO_2 , either $\text{Na}_2\text{S}_2\text{O}_4$ or Ag is preferred because of easy removal of insoluble NaAsF_6 or AgAsF_6 ; purification by fractional sublimation has been used for the more volatile radicals (87CC69). Since some derivatives of **3'** ($\text{R} = \text{Me}$, I) polymerize at high concentrations (>1 molal), it has not been possible to isolate the pure radicals, and so they are stored in solution.

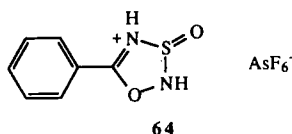
C. METATHESIS

The 1,3,2,4-dithiadiazolylum ring is usually prepared as the $[\text{AsF}_6]^-$ salt (Section XII). Other salts, e.g., of halides and $[\text{S}_3\text{N}_3]^-$ [91JCS(D)1099; 92JCS(D)1277], are readily prepared by metathesis with an appropriate tetraalkylammonium salt in CH_2Cl_2 or MeCN. Yields are generally greater than 60%.

D. HYDROLYSIS

The salts **3**⁺ and their solutions are generally highly sensitive to moisture, although salts with planar interacting anions may be expected to be more stable to hydrolysis (see **2**⁺ analogs, Section VI.B). The mechanism of hydrolysis of **[3][AsF₆]** ($\text{R} = \text{Ph}$) has been examined by ^1H nmr (92TH1) and would appear to initially involve a 2:1 stoichiometry (of $\text{H}_2\text{O} : [\text{3}][\text{AsF}_6]$). Equimolar ratios give only unreacted **[3][AsF₆]** and an unstable 2:1 hydrolysis product, proposed to be **64**. Further decomposi-

tion finally yields the acid amide PhCONH_2 with generation of SO_2 and loss of sulfur.



XVII. Preparation of 1,3,2,4-Dithiadiazolyls

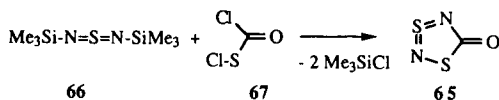
A. BY REDUCTION OF 1,3,2,4-DITHIADIAZOLYLIUM SALTS

Reduction of 3^+ salts with a variety of reducing agents is described in Section XVI.B and this is the major route to 3^{\cdot} radicals. There is, however, a second group of 1,3,2,4-dithiadiazolyls without free-radical character and these compounds have been prepared by several other routes, as outlined below.

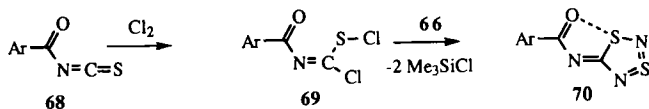
B. PREPARATION OF NONRADICAL 1,3,2,4-DITHIADIAZOLYLS

1. Condensation of Chlorosulphenyl Chlorides with Silylated Sulfur Diimides

The first neutral dithiadiazolyl to be prepared was $\text{O}=\overline{\text{CNSNS}}$, **65**, which can be formed by condensation of $\text{Me}_3\text{Si.NSN.SiMe}_3$ (**66**) with Cl.CO.SCl (**67**) (78CB698; 80CZ200).



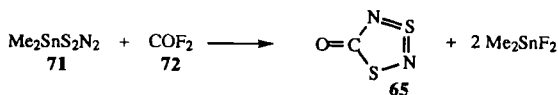
In an analogous manner, reactions of **66** with **69** (prepared by direct chlorination of an acyl isothiocyanate, Ar-C(=O)N=C=S , **68**) were found to form a series of aryl-substituted derivatives of **70**, ($\text{Ar}=\text{Ph}$, *p*-Me.C₆H₄, *m*- and *p*-Cl.C₆H₄, *p*-Br.C₆H₄, *p*-MeO.C₆H₄, *p*-O₂N.C₆H₄ and 2-naphthyl). The recovered yields of **70** were typically 70-77%. These



compounds are usually colourless, orange or yellow, unlike the darkly coloured 1,3,2,4-dithiadiazolyl radicals.

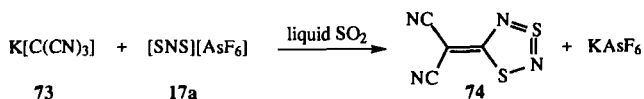
2. From $[\text{Me}_2\text{Sn}\overline{\text{NSNS}}]_2$ and a Halide

$\text{O}=\overline{\text{CNSNS}}$, **65**, was first prepared by Roesky and co-workers in 1975, using COF_2 and the tin reagent $[\text{Me}_2\text{Sn}\overline{\text{NSNS}}]_2$ [75AG(E)498; 75CZ433; 89IS49]. It was subsequently synthesised by the route described above.



3. From a Cyano Anion and $[\text{SNS}][\text{AsF}_6]$

The reaction of $\text{K}[\text{C}(\text{CN})_3]$ **73** with one equivalent of $[\text{SNS}][\text{AsF}_6]$ **17a** led to the neutral compound $(\text{NC})_2\text{C}=\overline{\text{CNSNS}}$ **74**, which can be crystallized as black prisms by high-vacuum sublimation (85°C , $10^{-7} \tau$) [92JCS(D)859]. Although it is esr-inactive, its dark lustrous appearance makes it somewhat anomalous for this group of materials.



XVIII. Physical Properties of 1,3,2,4-Dithiadiazolyls

Since such dithiadiazolyls may be either radical ($3'$) or spin-paired species (**3**), these two types show significant differences in their physical properties. With the exception of $(\text{NC})_2\text{C}=\overline{\text{CNSNS}}$, which is purple-black, the latter are lightly colored and tend to be moderately stable to hydrolysis. In contrast, the esr-active radicals $3'$ tend to be light-, heat-, and moisture-sensitive.

A. ELECTRON SPIN RESONANCE SPECTRA

Many 1,3,2,4-dithiadiazolyl radicals have been detected by solution esr spectroscopy. In accordance with MO calculations (Section XIII), these radicals show coupling to one nitrogen nucleus N' (farthest from the heterocyclic carbon) leading to a 1 : 1 : 1 triplet. Coupling to the second

nitrogen N'' (bonded to carbon) also occurs, but the coupling constants are very small ($\sim 1/20$ of $a_{N'}$). Isotropic g -values are normally in the region 2.005, with coupling constants to nitrogen, $a_{N'}$, in the order of 1.1 mT. Secondary couplings to alkyl and aryl substituents are also observed in some cases [83CC807; 85JCS(D)1405; 93UP9]. In the case of aryl derivatives, the strongest of these couplings is to substituents in the ortho position, as found for the isomeric species **2'** (Section IX.A). In the case of **3'** ($R = C_6F_5$), coupling to two equivalent fluorine nuclei is observed at room temperature (Fig. 20) [93UP9], indicating free rotation about the aryl-dithiadiazolyl bond, in a manner similar to that observed for the isomeric radical **2'** (Section IX.A). This is also in agreement with the nmr data for the parent salt **[3][SbCl₆]** ($R = C_6F_5$) [92JCS(D)3097], which shows only three ^{19}F resonances (Section XIV.A) indicative of rapid rotation around the aryl-dithiadiazolyl bond. A summary of esr data is given in Table XII.

For optimum resolution, the concentration of the parent salt must be minimized (by using an excess of reducing agent) to prevent appreciable electron exchange between **3⁺** and **3'**. The spectra should be recorded at low temperature to reduce spin-rotational relaxation [85JCS(D)1405] and also to minimize line-broadening through out-of-plane vibrations, such as those observed about the S—S axis [83JCS(F)925]. The temperature coefficients of the hyperfine coupling constants are in accord with an out-

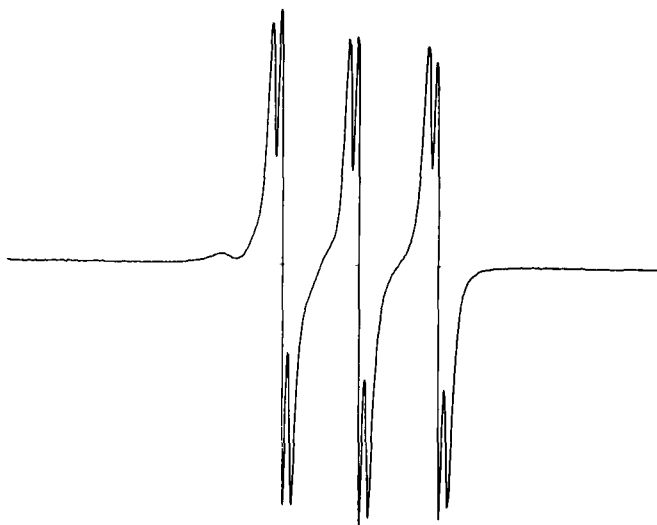
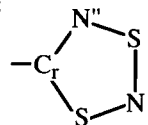


FIG. 20. First derivative X-band esr spectrum of $[C_6F_5.\overline{CNSNS}]^\bullet$ at 273K.

TABLE XII
ISOTROPIC ESR DATA FOR 1,3,2,4-DITHIADIAZOLYLS^a
(COUPLING CONSTANTS IN MILLI-TESLAS)

Substituent	Temperature (K)	Solvent	<i>g</i>	<i>a</i> _{N'}	<i>a</i> _{N''}	<i>a</i> _H	<i>a</i> _F	<i>a</i> _{S-33}	Reference
Me	221	MeCN		1.095	0.0644	0.0644			83CC807
Me	208	MeCN		1.086	0.066				85JCS(D)1405
Me	172	THF		1.100	0.063				85JCS(D)1405
Me	234	<i>d</i> ₈ -toluene	2.00532	1.101	0.0439				85JCS(D)1405
CF ₃		SO ₂ /CFCl ₃	2.0057	1.11					86CC140
I		SO ₂ /CFCl ₃	2.0048	1.12	0.06				86CC140
<i>t</i> Bu			2.0071	1.09	0.06				87CC69
<i>t</i> Bu	188	<i>d</i> ₈ -toluene	2.0048	1.094	0.0525			0.479	92MRC666
Ph	298	toluene	2.006	1.12					93UP9
<i>p</i> -F.C ₆ H ₄	298	toluene	2.006	1.11					93UP12
<i>m</i> -F.C ₆ H ₄	298	toluene	2.006	1.10					93UP12
<i>o</i> -F.C ₆ H ₄	298	toluene	2.005	1.08					93UP12
C ₆ F ₅	298	toluene	2.005	1.11			0.06		93UP12

^a Heterocyclic coupling constants refer to the following atom labeling scheme:



of-plane bend about the S—S vector, leading to a positive value for a_N , while other coupling constants are negative [83JCS(FI)925]. In the case of the most extensively studied radical of this type, 3^{\cdot} ($R = \text{Me}$), the observed hyperfine couplings are in good agreement with INDO and Gaussian MO calculations (Section XIX).

B. MAGNETIC DATA

Owing to the thermal and photochemical sensitivity of the radicals (Section XXI.A) and, in some cases, the possibility of polymerization at high concentration (Section XXI.B), the data on pure samples are limited. The only magnetic data currently available for 1,3,2,4-dithiadiazolyl radicals are for 3^{\cdot} ($R = t\text{Bu}$); at room temperature this compound is a brown liquid, with an effective magnetic moment of $1.5 \mu_B$ (87CC69), somewhat less than the anticipated value for a single unpaired electron of $1.73 \mu_B$. Nevertheless, this material can be described as a paramagnetic liquid as it is virtually dissociated in the liquid state (see also Section IX.D).

XIX. Theoretical Studies of 1,3,2,4-Dithiadiazolyl Radicals

The geometries and esr coupling constants of the radical 3^{\cdot} ($R = \text{Me}$) and also the parent cation 3^+ (Section XIII) have been compared with data from INDO molecular orbital calculations [85JCS(D)1405].

For the cation, the calculated bond distances and angles differ quite markedly from the X-ray data [85JCS(D)1405] (Section XV, Table XI). However, partial occupancy of the predominantly antibonding 3^+ LUMO (Section XIII) should lead to an increase in C—S and S—N bond distances. Although there are no X-ray structural data available for any mono-1,3,2,4-dithiadiazolyls, the crystal structure of the diradical [$p\text{-C}_6\text{H}_4(\overline{\text{CNSNS}})_2$] (Section XXIII.E) shows that these distances do indeed increase, compared to the dication, but appreciable discrepancies still exist between theoretical and experimental data sets.

In contrast, there is excellent agreement between the predicted esr coupling constants for 3^{\cdot} ($R = \text{Me}$) and the experimental data.

Molecular orbital studies on the orbital interactions between two 3^{\cdot} radicals have been carried out (86CC140) in order to rationalize the rearrangement mechanism (Section XXI.A.1) by which 3^{\cdot} is converted to 2^{\cdot} in solution. These studies show that the SOMO, which is of π character, has the largest coefficients on the sulfur atoms, and thus association can be considered to arise through S . . . S bonding interactions. Coupled

with the dipole moment inherent with the nonsymmetric radicals $3'$, a cofacial head-to-tail mechanism was proposed (further evidence indicates that this is the likely mechanism; see Section XXIII.G.3), which also allows for weaker C . . . N interactions. Furthermore, careful study of the MOs of $2'$ and $3'$ (87CC69) shows that the rearrangement process is thermally symmetry-forbidden but photochemically symmetry-allowed. In practice, radicals with bulkier substituents tend to be thermally stable, whereas other derivatives spontaneously rearrange (Section XXI.A.1).

In conclusion, open-shell MO calculations on $3'$ radicals can provide good qualitative comparisons with empirical results (especially esr data), but quantitative conclusions may not be reliable.

XX. X-Ray Diffraction Studies of 1,3,2,4-Dithiadiazolyls

To date, the only structures of 1,3,2,4-dithiadiazolyls to be determined by X-ray crystallography have been those of the spin-paired, diamagnetic dithiadiazolyls: OCNSNS **65**, $p\text{-Me.C}_6\text{H}_4.\text{C}(=\text{O})\text{NCNSNS}$ **70**, and $(\text{NC})_2\text{C}\overline{\text{CNSNS}}$ **74** (Fig. 21) in particular. Table XIII shows their heterocyclic bond lengths and angles. Of the three structures so far reported, the least perturbed would appear to be **74**, although this molecule itself shows extensive secondary contacts forming molecular sheets held together through $\text{CN}^{\delta-} \cdots \text{S}^{\delta+}$ interactions [92JCS(D)859].

In the case of **70** ($\text{R} = p\text{-Me.C}_6\text{H}_4$) (78CB698), modification of the heterocyclic ring distances occurs in the CSN heterocyclic fragment of the ring: secondary bonding interactions between S(1) and the exocyclic oxygen lead to a corresponding weakening of the ring C—S(1) and S(1)—N(1) bonding contributions. This is coupled with an associated strengthening of the other heterocyclic bonds. In comparison, strong $\text{C}=\text{O}$ bonding in **65** leads to a weakening of both C—N and C—S bonding contributions, and thus this material is best written with a formal double bond, **65a**, and not as the zwitterion **65b** (78CB1670).

TABLE XIII
HETEROCYCLIC BOND DISTANCES FOR 1,3,2,4-DITHIADIAZOLYLS

Compound	Bond Distance (Å)					Reference
	C—N''	N''—S''	S''—N'	N'—S'	S'—C	
$\text{O}=\overline{\text{CNSNS}}$	1.374(7)	1.584(4)	1.572(5)	1.630(4)	1.813(5)	78CB1670
$(\text{NC})_2\text{C}=\overline{\text{CNSNS}}$	1.352(4)	1.588(3)	1.576(3)	1.630(3)	1.766(3)	92JCS(D)859
$\text{MeC}_6\text{H}_4\text{CON}=\overline{\text{CNSNS}}$	1.351	1.580	1.555	1.659	1.788	78CB698

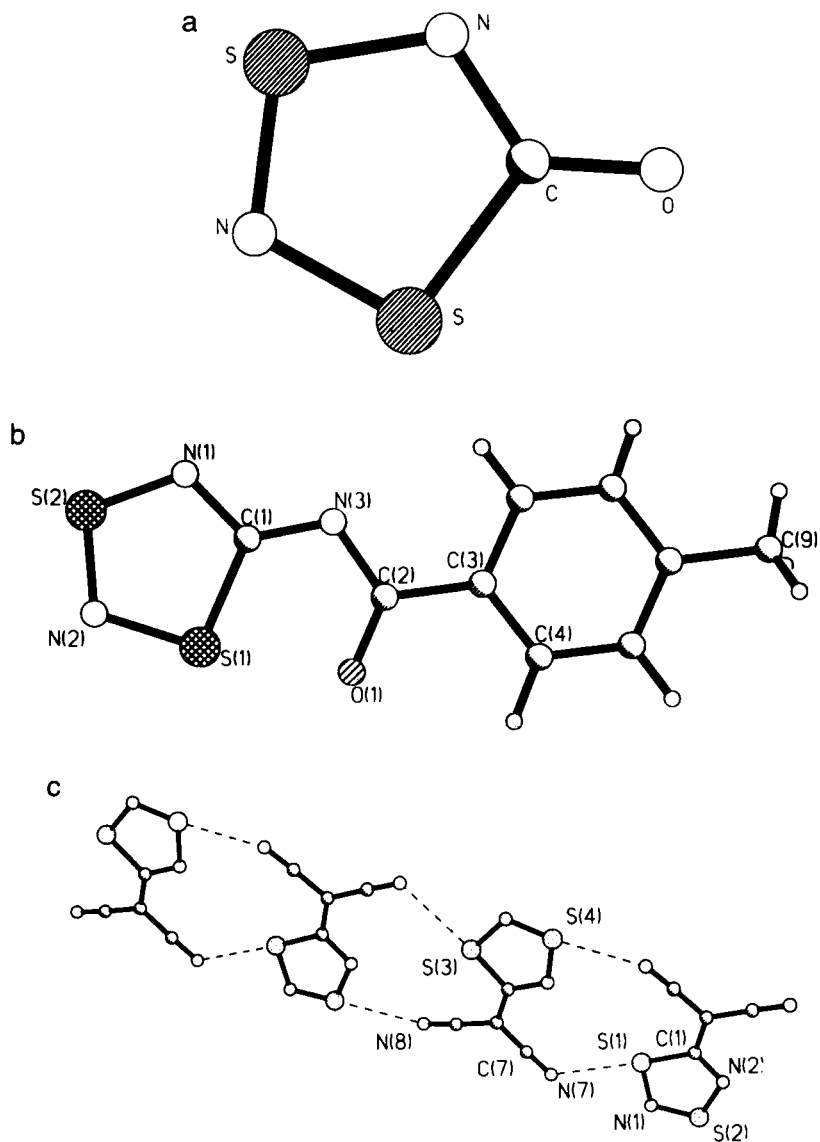
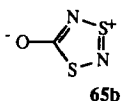
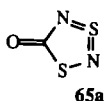


FIG. 21. Crystal structures of (a) $\text{O}=\overline{\text{CNSNS}}$ and (b) $p\text{-Me.C}_6\text{H}_4\text{CO.N}=\overline{\text{CNSNS}}$; (c) molecular packing diagram for $(\text{NC})_2\text{C}=\overline{\text{CNSNS}}$.



Compared with **65** and **70**, **74** would appear to be more delocalized in nature (which may lead to its greater luster). The X-ray data do not show any strong *intramolecular* secondary bonding modes such as those that lead to the structural distortions observed in **65** and **70**. In solid **74**, the in-plane *intermolecular* $\text{—C}\equiv\text{N} \cdots \text{S}$ interactions link the molecules together into planar sheets. These sheets are further linked by slightly weaker out-of-plane $\text{—C}\equiv\text{N} \cdots \text{S}$ interactions.

XXI. Reactivity of 1,3,2,4-Dithiadiazolyls

As previously mentioned, the spin-paired and radical species (**3** and **3'**) exhibit significantly different chemistries, and this is highlighted in their differing physical properties such as their esr behavior (Section XVIII.A). This difference is carried through to their reactivities, and so their chemical properties will be described separately.

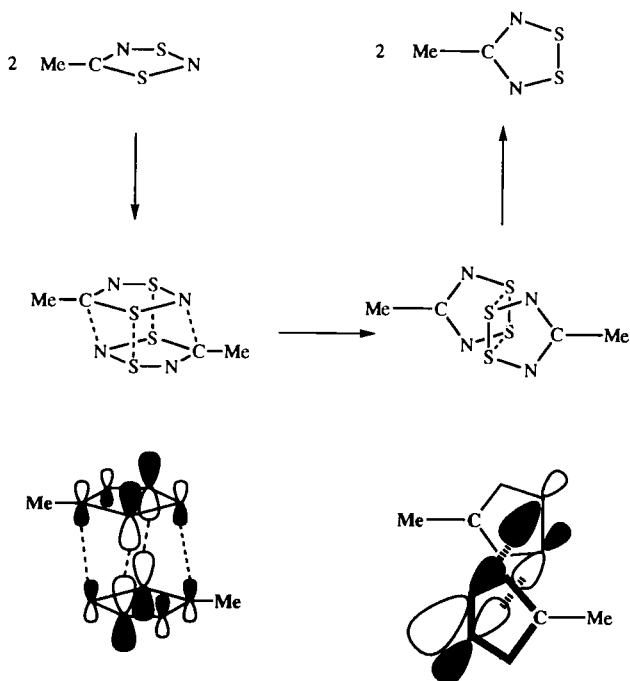
A. REACTIVITY OF 1,3,2,4-DITHIADIAZOLYL RADICALS

Since these materials (Table XIII) are usually unstable, their chemistry has primarily been limited to rearrangement and polymerization reactions.

1. Rearrangement

The major reaction of **3'** derivatives is rearrangement from **3'** to their isomeric counterparts **2'** [86CC140; 87CC69; 92MRC666]. This rearrangement process was studied by esr spectroscopy and found to be second-order with respect to the radical concentration (86CC140). Dipole moments and SOMO overlap (through $\text{S} \cdots \text{S}$ and, to a lesser extent, $\text{C} \cdots \text{N}$ interactions) suggest that the bimolecular head-to-tail cofacial dimer (Scheme 12) is the most favorable conformation that facilitates rearrangement. (This proposed conformation has also been found in the solid-state structure of $[p\text{-C}_6\text{H}_4(\overline{\text{CNSNS}})_2]$, which undergoes thermal rearrangement in the solid state to form the isomeric $[p\text{-C}_6\text{H}_4(\overline{\text{CNSNS}})_2]$ (Section XXIII.G.3)).

The solution-state rearrangement can be conveniently monitored by esr; a three-line 1 : 1 : 1 triplet (Section XVIII.A) is replaced over a period

SCHEME 12. Isomerization of $[\text{Me}.\overline{\text{CNSNS}}]$ to $[\text{Me}.\overline{\text{CNSSN}}]$

of time by a 1 : 2 : 3 : 2 : 1 pentet (Section IX.A). In some cases, where the substituent is small ($\text{R} = \text{Me}$, CF_3 , or I) rearrangement occurs rapidly at room temperature (86CC140), whereas more bulky radicals (with $\text{R} = t\text{Bu}$, Ar) would appear indefinitely stable in the dark (at room temperature). These radicals rapidly isomerize on irradiation. These observations, together with an examination of the frontier molecular orbitals of 2^\cdot and 3^\cdot imply that the process is thermally symmetry-forbidden but photochemically symmetry-allowed (87CC69).

2. Polymerization

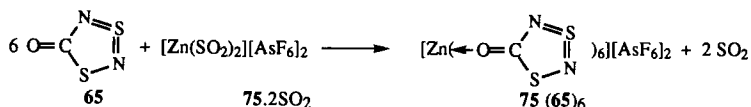
Although some of the thermally stable derivatives of 3^\cdot (e.g., $t\text{Bu}$) can be isolated in a pure state (if kept in the dark) (87CC69), other radicals, particularly 3^\cdot ($\text{R} = \text{Me}$, I), form intractable brown polymers at high concentrations (>1 molal). The nature of such polymeric materials is unknown.

B. REACTIVITY OF NONRADICAL 1,3,2,4-DITHIADIAZOLYLS

Unlike **3'**, spin-paired derivatives **3** show no tendency to undergo rearrangement in solution (or even on heating in the solid state [92JCS(D)1277]; see the diradicals described in Section XXIII.G.3). In fact, such materials appear significantly more stable and their chemistries more diverse.

1. Adduct Formation

The spin-paired dithiadiazolyis are not readily oxidized to radical cations **3**⁺. Reaction of OCNSNS **65** with a variety of Lewis acids (AsF_5 , SbF_2Cl_3 , SbCl_5 , SO_3 , and BF_3) did not produce any $[\mathbf{3}^+]\text{X}$ salts ($\text{X} = \text{AsF}_6^-$, etc.) (contrast the behavior of **2'**; Section XI.A), but rather 1 : 1 adducts $[\mathbf{65}]\text{.A}$ ($\text{A} = \text{BF}_3$, etc.). Similarly, reaction with SnCl_4 and TiCl_4 gave the 2 : 1 adducts, $[\mathbf{65}]_2\text{.MCl}_4$ ($\text{M} = \text{Sn, Ti}$) (78CB1670). Infrared spectra of these compounds indicate that **65** is bonded to the metal via the exocyclic oxygen in preference to either ring N or S atoms. The X-ray structure of the AsF_5 adduct shows, unambiguously, that **65** is coordinated via the exocyclic oxygen (Fig. 22) (80CB3904).



In a similar manner, **65** acts as a neutral ligand, coordinating to metal ions in preference to SO_2 ; thus the reaction of $[\text{Zn}(\text{SO}_2)_2][\text{AsF}_6]_2$ (**75.2SO₂**) with **65** leads to loss of SO_2 and the formation of $[\text{Zn}(\text{OCNSNS})_6][\text{AsF}_6]_2$.

The structure of this compound (Fig. 22) shows preferential coordination through the exocyclic oxygen [82AG(E)858; 82AG(S)1813]. Adduct formation of this type leads to a weakening of the $\text{C}=\text{O}$ bond and hence a shortening of the heterocyclic bonds as the compound becomes more delocalized. No adducts of the other 1,3,2,4-dithiadiazolyis have yet been reported.

2. Alkylation

Reaction of **70** with methyl fluorosulfonate FSO_2OMe **76** leads to methylation of the exocyclic carbonyl oxygen atom (78CB698), whereas methylation of **65** with $[\text{MeOSO}][\text{AsF}_6]$ **77** leads to alkylation of the ring nitrogen adjacent to the carbonyl group (80CB2802).

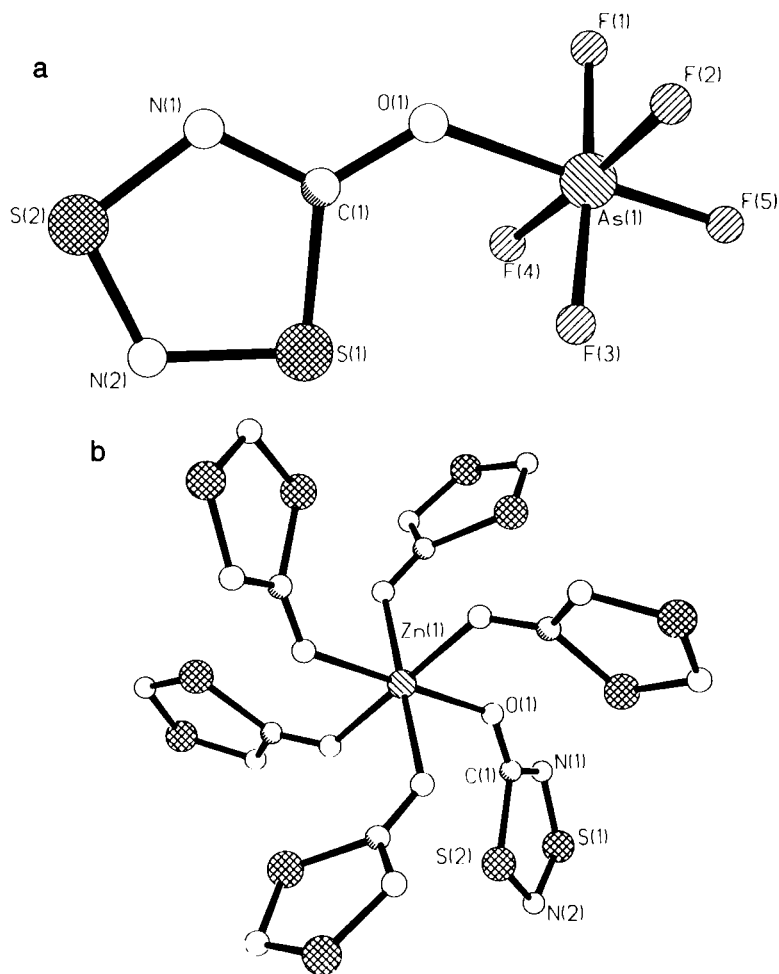


FIG. 22. Crystal structures of (a) $\text{O}=\overline{\text{CNSNS}}\cdot\text{AsF}_5$ and (b) the cation in $\text{Zn}(\overline{\text{OCNSNS}})_6\cdot(\text{AsF}_6)_2$.

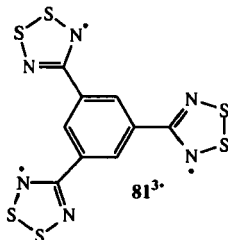
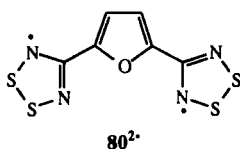
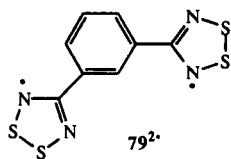
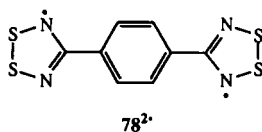
XXII. Multi-1,2,3,5-dithiadiazolylium Salts and Dithiadiazolyls

A. PREPARATION OF MULTI-1,2,3,5-DITHIADIAZOLYLIUM SALTS

Multi-1,2,3,5-dithiadiazolylium salts can be prepared in a manner analogous to 2^+ salts; in particular, by (i) condensation of amidines with SCl_2 and (ii) reaction of nitriles with ammonium chloride and SCl_2 .

1. Reaction of Amidines with SCl_2

The bis- and trisdithiadiazolylium salts, $[\mathbf{78}\text{--}\mathbf{80}]\text{Cl}_2$ and $[\mathbf{81}]\text{Cl}_3$ can be prepared by reaction of the parent multinitrile with two or three equivalents of $\text{Li}[\text{N}(\text{SiMe}_3)_2]/\text{Me}_3\text{SiCl}$ in diethyl ether (to generate the persilylated amidine; see Section II.C), followed by condensation with a slight stoichiometric excess of SCl_2 (89JA9276; 91JA582; 91JA3559; 92CJC919; 92JA5000).



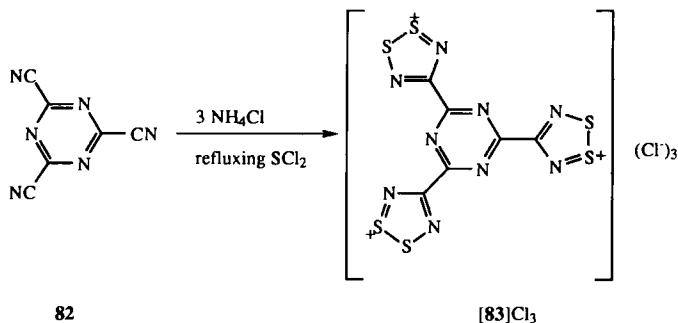
In most cases the chloride salts were not isolated but were directly reduced directly to the free radical. However, yields of the chloride can be assumed to be in excess of 50%. Oakley and co-workers have reported that the selenium analogs can be prepared in an analogous manner (89JA9276; 91JA582; 91JA3559; 92JA5000).

2. Reaction of Nitriles with Ammonium Chloride and SCl_2

The reaction of simple nitriles with ammonium chloride and SCl_2 under a chlorine atmosphere (Section II.B) has previously been shown to yield $[\mathbf{2}]\text{Cl}$ in moderate yields. However, reaction of *p*-dicyanobenzene with ammonium chloride in refluxing SCl_2 (or directly with $\mathbf{11}$) has been reported to yield only small quantities ($\sim 1\%$) of $[\mathbf{2}]\text{Cl}$ ($\text{R} = p\text{-NC}_6\text{H}_4$) within the SO_2 -soluble fraction, and no $[\mathbf{78}]\text{Cl}_2$ was observed [91JCS(D)1099].

Recent work has shown that in cases where the silylated amidines are not readily accessible, e.g., tricyano-*sym*-triazine $\mathbf{82}$ (where addition of $\text{Li}[\text{N}(\text{SiMe}_3)_2]$ leads to nucleophilic attack at the triazine carbon atoms (93IC1554)), this route may be utilized instead.

The required salt $[\mathbf{83}]\text{Cl}_3$ was formed after refluxing in SCl_2 for four



days in unspecified yield (but >12% based on the isolated yield of purified radical **83**³). Sulfur–nitrogen-based impurities, predominantly **11** and **26**, can be readily chlorinated and then washed out from the product mixture with CH₂Cl₂.

B. CHEMICAL AND PHYSICAL PROPERTIES OF MULTI-1,2,3,5-DITHIADIAZOLYLIUM SALTS

All of the multi-1,2,3,5-dithiadiazolium salts studied to date possess two or more heterocyclic rings, separated by aromatic spacer groups, i.e., phenylene, furyl, benzene-triyl, or *sym*-triazine-triyl. To a first approximation, these heterocycles are noninteracting, and consequently the multications chemically resemble analogous 2⁺ salts (see Sections IV and VI).

1. Anion Metathesis Reactions

[**78**]Cl₂ undergoes metathesis reactions with two equivalents of [NO][SbF₆] [89JA9276; 90AX(C)140] to give [**78**][SbF₆]₂. These salts should also undergo the extensive anion exchange and addition chemistry of [2]⁺ salts and of the isomeric multi-1,3,2,4-dithiadiazolium salts (Section XXIII.B.2).

2. Electrochemical Studies

[**78**][SbF₆]₂ exhibits electrochemical behavior similar to [2]X salts, showing only one broad two-electron reduction peak, indicative of two noninteracting rings (89JA9276).

C. X-RAY DIFFRACTION STUDIES OF MULTI-1,2,3,5-DITHIADIAZOLYLIUM SALTS

The crystal structure of **[78]** $[\text{SbF}_6]_2$ as the bisbenzonitrile solvate (Fig. 23) **[90AX(C)140]** shows dimensions in the heterocyclic ring similar to the corresponding derivatives of $[2]^+$ with hard anions, e.g., $d_{\text{CN}} = 1.34(1)$, $d_{\text{NS}} = 1.577(9)$, and $d_{\text{SS}} = 2.009(4)\text{\AA}$ (see Table IV, Section V). The selenium analog has been crystallized as the trisbenzonitrile solvate **[90AX(C)699]**.

D. PREPARATION OF MULTI-1,2,3,5-DITHIADIAZOLYL RADICALS

Reduction of any of the salts **[78–80]** Cl_2 , **[81]** Cl_3 , or **[83]** Cl_3 with a slight stoichiometric excess of Ph_3Sb in acetonitrile yields the corresponding multiradical, typically as a fine, highly insoluble black microcrystalline precipitate. Because of the low solubility of these multiradicals in most organic solvents, side products (Ph_3SbCl_2 and unreacted Ph_3Sb) can be washed out readily and the multiradicals crystallized by vacuum sublimation, typically at $\sim 150^\circ\text{C}/10^{-2}\tau$ for the diradicals and $\sim 270^\circ\text{C}/10^{-2}\tau$ for the triradicals.

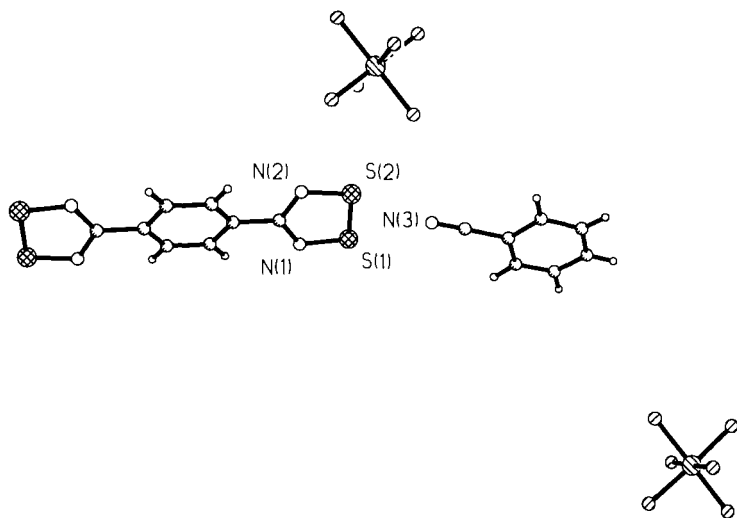


FIG. 23. Crystal structure of $[p\text{-C}_6\text{H}_4(\overline{\text{CNSSN}})_2][\text{SbF}_6]_2 \cdot 2\text{PhCN}$ showing one of the solvent molecules.

E. X-RAY DIFFRACTION STUDIES OF MULTI-1,2,3,5-DITHIADIAZOLYL RADICALS

Multi-1,2,3,5-dithiadiazolyl radicals fall into two distinct categories: those forming discrete dimeric pairs (in which electron pairing at both heterocyclic rings produces an enforced cis-oid configuration, analogous to their [2]₂ counterparts; Section X.B.2), and those forming columnar polymeric arrays held together through sets of long and short secondary S . . . S interactions. Discrete dimeric pairs are formed by **78**^{2•}, **80**^{2•}, and **83**^{3•} (Figure 24), whereas **79**^{2•} and **81**^{3•} crystallize as polymeric arrays.

Within each radical unit, heterocyclic bond distances and angles (Table XIV) are remarkably similar for both structural types. The structural differences between these radicals must, therefore, be attributable to competition between intrastack (favoring columnar polymeric arrays) and interstack (favoring discrete dimeric pairs) secondary interactions (93IC1554). Intrastack interactions are favored when increasing the number of radicals per formula unit (i.e., increasing the number of columnar interactions), but this is counteracted in the case of **83**^{3•} where in-plane interactions between heterocyclic sulfur atoms and triazine nitrogen atoms lead to a dimeric structure. This fine balance between dimeric and polymeric arrays is highlighted by the selenium analog of **79**^{2•}, i.e., *m*-C₆H₄($\overline{\text{CNSeSeN}}$)₂, which exhibits polymorphism (92JA1729): the α -phase is isostructural with the polymeric **79**^{2•}, while a second β -phase consists of discrete dimeric pairs held together through in-plane and out-of-plane secondary Se . . . Se contacts.

F. PHYSICAL PROPERTIES OF MULTI-1,2,3,5-DITHIADIAZOLYL RADICALS

1. Electron Spin Resonance Spectra

At low temperature (-60°C) the solution spectra of **78**^{2•} and **79**^{2•} show the expected 1:2:3:2:1 pentet associated with noninteracting 1,2,3,5-dithiadiazolyl units (see Section IX.A): for **78**^{2•} and **79**^{2•}, $g = 2.011$, $a_{\text{N}} = 0.51$ mT in CHCl₃. (No solution esr data have been reported for **80**^{2•}, **81**^{3•}, or **83**^{3•}, possibly due to their extremely low solubility in organic media.) However, as the temperature is raised to $+60^{\circ}\text{C}$, a second set of resonances at $a_{\text{N}}/2$ is observed, indicative of spin-spin exchange between radical centers (91JA582; 91JA3559). Because of the low solubility of these radicals, the exchange mechanism may be a weak intramolecular process, modulated by rotation about the phenylene-dithiadiazolyl bond.

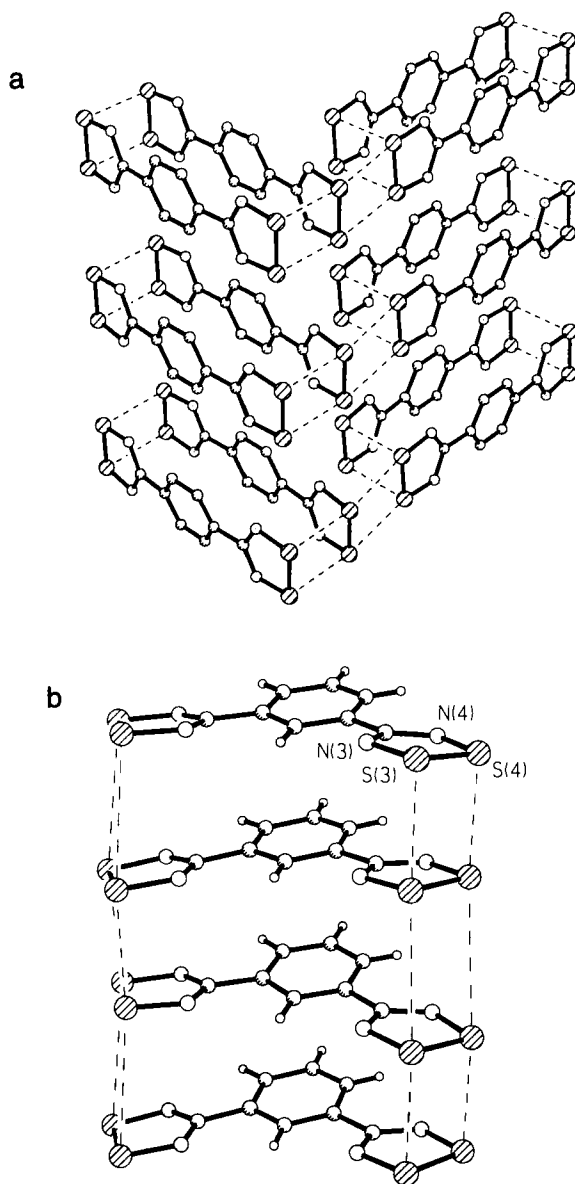


FIG. 24. Molecular packing of (a) [*p*-C₆H₄($\overline{\text{CNSSN}}$)₂], (b) [*m*-C₆H₄($\overline{\text{CNSSN}}$)₂], (c) [*sym*-C₆H₃($\overline{\text{CNSSN}}$)₃], and (d) [*sym*-C₃N₃($\overline{\text{CNSSN}}$)₃].

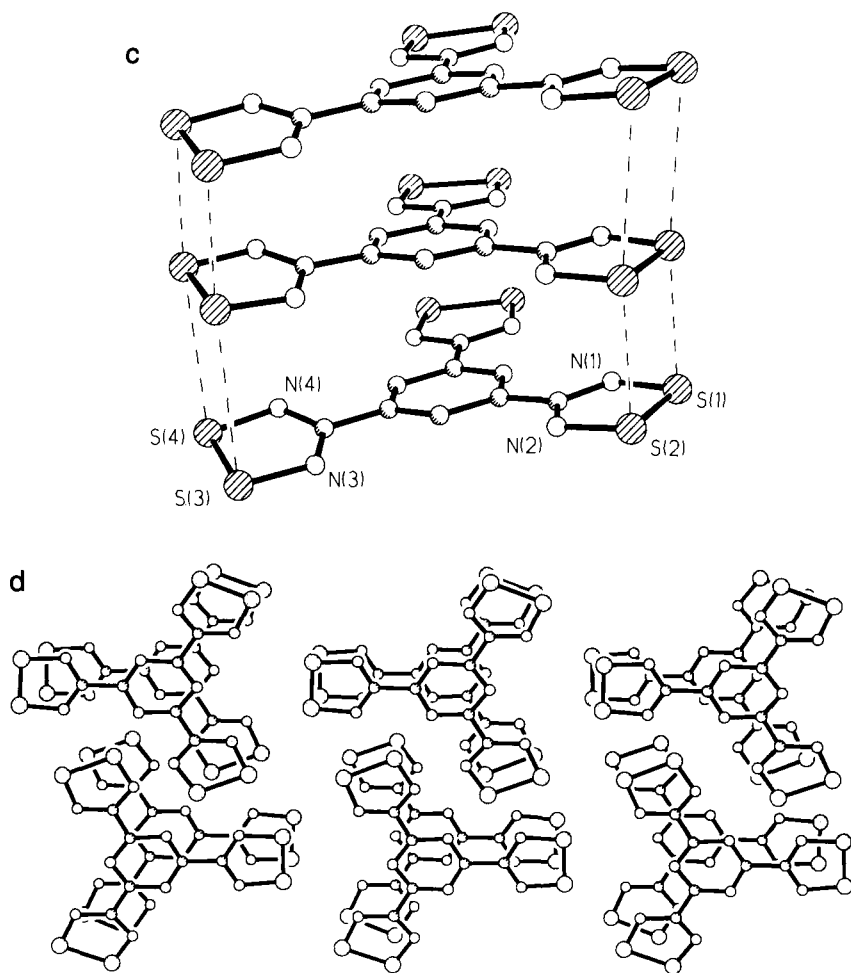


FIG. 24. (Continued)

Single-crystal solid-state esr studies on **79**²⁻ have shown that the number of unpaired spins per molecule is less than 1% (91JA3559), which implies that these paramagnetic impurities are, in fact, unpaired molecules of **79**²⁻, located at lattice defects. These unpaired radicals show a well-resolved 1:2:3:2:1 pentet ($g_{zz} = 2.0021$, $a_{N_{zz}} = 1.331$ mT) at 9K (with the magnetic field perpendicular to the c axis).

TABLE XIV
HETEROCYCLIC BOND DISTANCES (Å), ANGLES (°), AND SECONDARY CONTACTS (Å) FOR
MULTI-1,2,3,5-DITHIADIAZOLYLS

	Compound				
	78 ²	79 ²	80 ²	81 ³	83 ³
S—S (Å)	2.099	2.084	2.089	2.085	2.105
N—S (Å)	1.638	1.627	1.633	1.631	1.628
C—N (Å)	1.333	1.340	1.336	1.338	1.326
N—S—S (°)	94.4	94.6		94.7	94.1
C—N—S (°)	114.0	114.3		113.9	114.1
N—C—N (°)	123.4	122.0		122.9	123.6
Short S . . . S ^a	3.121	3.140	3.137	3.117	2.872–3.225
Long S . . . S	—	3.966	—	3.837	—
Reference	91JA582	91JA3559	92CJC919	92JA5000	93IC1554

^a Mean S . . . S distances are quoted for 78² and 80². Compound 83³ possesses a wide range of intradimer contacts and this range is stated. Compounds 79² and 81³ consist of polymeric stacks held together through long and short contacts—the mean of the short contacts is quoted here.

2. Magnetic Susceptibility

As the solid-state structures of all of these multi-1,2,3,5-dithiadiazolyl radicals reveal strong spin-paired interactions, it is to be expected that these multiradicals (like their monofunctional counterparts) are predominantly diamagnetic in the solid state, with only a small number of unpaired electrons per molecule (<1%). This is in good agreement with the figures determined by esr. At and below room temperature the few unpaired spins follow a Curie–Weiss temperature dependence ($1\text{K} \leq \theta \leq 7\text{K}$) (91JA582; 91JA3559; 92JA5000; 93IC1554). However, in some cases, most noticeably 79², an unusual susceptibility is observed at elevated temperatures: on warming from room temperature to 50°C, there is a decrease in magnetic susceptibility which has been attributed (91JA3559) to annealing of the sample (removing some of the lattice defects). On further warming, breakdown of the lattice starts to occur, and there is an accompanying increase in susceptibility as the number of defects begins to rise again. For samples of 79² and 81³ (with polymeric structures), slight hysteresis is observed at elevated temperatures, and this has been attributed (92JA5000) to the generation of phase kinks in the lattice on warming and cooling.

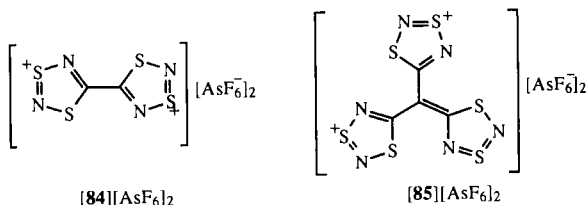
3. Conductivity

Like their mono-1,2,3,5-dithiadiazolyl analogs, the majority of multi-1,2,3,5-dithiadiazolyl radicals are also insulators with conductivities at room temperature $\leq 10^{-9}$ S/cm. However, **81**³, which forms the tightest polymeric stacks, has the greatest conductivity of these materials to date: $\sim 10^{-7}$ S/cm at room temperature, rising to 10^{-4} S/cm at 600K. In comparison, many of the selenium analogs of these materials are semiconductors at room temperature, with $10^{-4} \leq \Lambda \leq 10^{-2}$ S/cm (91JA582; 91JA3559).

XXIII. Multi-1,3,2,4-dithiadiazolylium Salts and Dithiadiazolyls

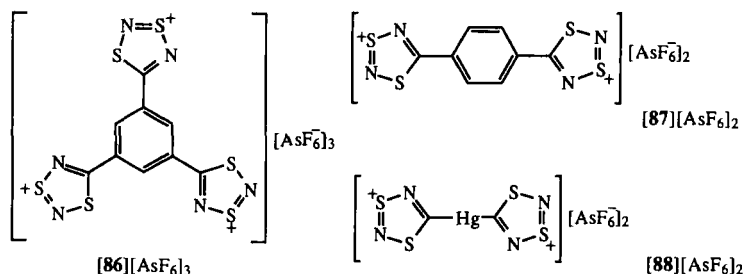
A. PREPARATION OF MULTI-1,3,2,4-DITHIADIAZOLYLIUM SALTS

Reaction of [SNS][AsF₆] **17a** with a variety of multicyano-substituted molecules (e.g., phenylene and biphenylene derivatives, dicyanogen, potassium tricyanomethanide, and mercury(II)cyanide) has led to the isolation of a series of multi-1,3,2,4-dithiadiazolylium salts in high recovered yield (typically >70%) [91CC369; 91JCS(D)1099; 92JCS(D)859; 92JCS(D)1277; 92JPS(A)2653; 93JCS(D)1499; 94CC29] exemplified by the salts of cations of **84**–**88**. These reactions have recently been summarized [93JCS(D)1421].



With the exception of dicyanogen (50°C, 5 days), these cycloaddition reactions proceed smoothly in 18–36 hours at room temperature in liquid SO₂. In the majority of phenylene derivatives, the nitrile groups are spatially well-separated, and any earlier cycloadditions do not greatly perturb the ionization potentials of unreacted cyanide groups. Such reactions proceed smoothly to give the fully substituted products only. This was also the case in the formation of **[84]**[AsF₆]₂; the intermediate system **[3]**[AsF₆] (R = CN) could not be isolated [93JCS(D)1499]. However, in the reaction of **17a** with K[C(CN)₃] **73**, leading ultimately to the formation of **[85]**[AsF₆]₂, both of the intermediate cycloaddition products were isolated [92JCS(D)859].

Such important differences in reactivity have been rationalized using MO/ionization potential considerations [92JCS(D)859; 93JCS(D)1499]. With both NC.CN and $[\text{C}(\text{CN})_3]^-$, an important step in the reaction pathway would appear to be an electrostatic interaction between SNS^+ and the heterocyclic nitrogen in the intermediate 1,3,2,4-dithiadiazolyl/ium (bound to carbon), leading to (i) modification of orbital energies and (ii) an asynchronous cycloaddition mechanism (see Section XII.B).



B. CHEMICAL AND PHYSICAL PROPERTIES OF MULTI-1,3,2,4-DITHIADIAZOLYL IUM SALTS

1. As Cationic Initiators for the Polymerization of THF

The use of $3[\text{AsF}_6]$ as a cationic initiator for the polymerization of THF has been described in Section XVI.A. Further work has shown that the related multi-1,3,2,4-dithiadiazolyl cations, in as $\text{86}[\text{AsF}_6]_3$, and $\text{87}[\text{AsF}_6]_2$ also act as initiators in a similar fashion [92JPS(A)2653]. Although no kinetic data are available, polymerization using these reagents (e.g., $\text{86}[\text{AsF}_6]_3$) appears to be superior to the monocationic salts, since it gives clear viscous gels in much shorter time periods while maintaining a low polydispersity (1.61) and high molecular weight ($190,000 \text{ g mol}^{-1}$).

2. Metathesis and Addition Reactions

With all but the hardest of anions, multi-1,3,2,4-dithiadiazolyl cations have poor solubility in most solvents; consequently, many salts have been prepared in high yields ($>70\%$) in ways similar to the salts $[\text{2}]\text{X}$ (Section VI.A) [91JCS(D)1099; 92JCS(D)859; 92JCS(D)1277; 93JCS(D)1499]. For example, $\text{87}[\text{AsF}_6]_2$ reacts with two equivalents of $[\text{NBu}_4]\text{Cl}$ in organic solvents to give $[\text{87}]\text{Cl}_2$ as an insoluble yellow powder. $[\text{87}]\text{Cl}_2$ can then undergo an addition reaction with SbCl_5 to form $[\text{87}][\text{SbCl}_6]_2$ [91JCS(D)1099].

3. *Electrochemical Studies*

In a manner analogous to the multi-1,2,3,5-dithiadiazolylium salts (Section XXII.B.2), the phenylene and biphenylene bridged multi-1,3,2,4-dithiadiazolylium derivatives show remarkably similar electrochemical behavior to 3^+ salts. Although $[87][AsF_6]_2$ was reported to have two reversible reduction potentials (within 0.05 V) [91JCS(D)1099], this was subsequently found (93UP2) to be due to contamination of $[87][AsF_6]_2$ with small quantities of $[3][AsF_6]$ ($R = p\text{-NC}_6\text{H}_4$), which has a predicted [93JCS(D)967] half-wave reduction potential within 0.005 V of $[87][AsF_6]_2$.

In contrast, species with dithiadiazolylium rings in close proximity, e.g., $[84][AsF_6]_2$ and $[85][AsF_6]_2$, show strong intramolecular electron correlation and have two discrete, one-electron, reversible reductions to the radical cation and the diradical [92JCS(D)859].

C. X-RAY DIFFRACTION STUDIES OF MULTI-1,3,2,4-DITHIADIAZOLYLIUM SALTS

Three structures have been determined for this class of material; however, none are of the most common phenylene-bridged systems. The structures of $[84][AsF_6]_2$, $[85][AsF_6]_2$, and the mercury-bound salt $[88][AsF_6]_2$, are shown in Figure 25. The bond distances and angles (Table XV) are similar to those reported for the monosubstituted derivatives, $[3][AsF_6]$ (Section XV).

D. PREPARATION OF MULTI-1,3,2,4-DITHIADIAZOLYL RADICALS

These radicals can be prepared readily by reduction of the corresponding 1,3,2,4-dithiadiazolylium salts in a manner analogous to that described for 3^+ (Section XVII.A). Radicals prepared by reduction of $[84][AsF_6]_2$ rearrange readily at room temperature over a period of minutes [93JCS(D)1499], as found for many of the derivatives of 3^+ . In contrast, the phenylene derivatives (e.g., $86^{3\cdot}$ and $87^{2\cdot}$) and the biphenylene derivatives (such as $89^{2\cdot}$) appear to be indefinitely stable at ambient temperature, and this stability has allowed many of them to be isolated as solids [91JCS(D)1099; 92JCS(D)1277]. Because of extremely low solubility in organic solvents, reduction of the chloride salt with $SbPh_3$ allows for separation of the insoluble radical from Ph_3SbCl_2 . (*N.B.*: Continuous extraction of the crude product with SO_2 or MeCN is sometimes required

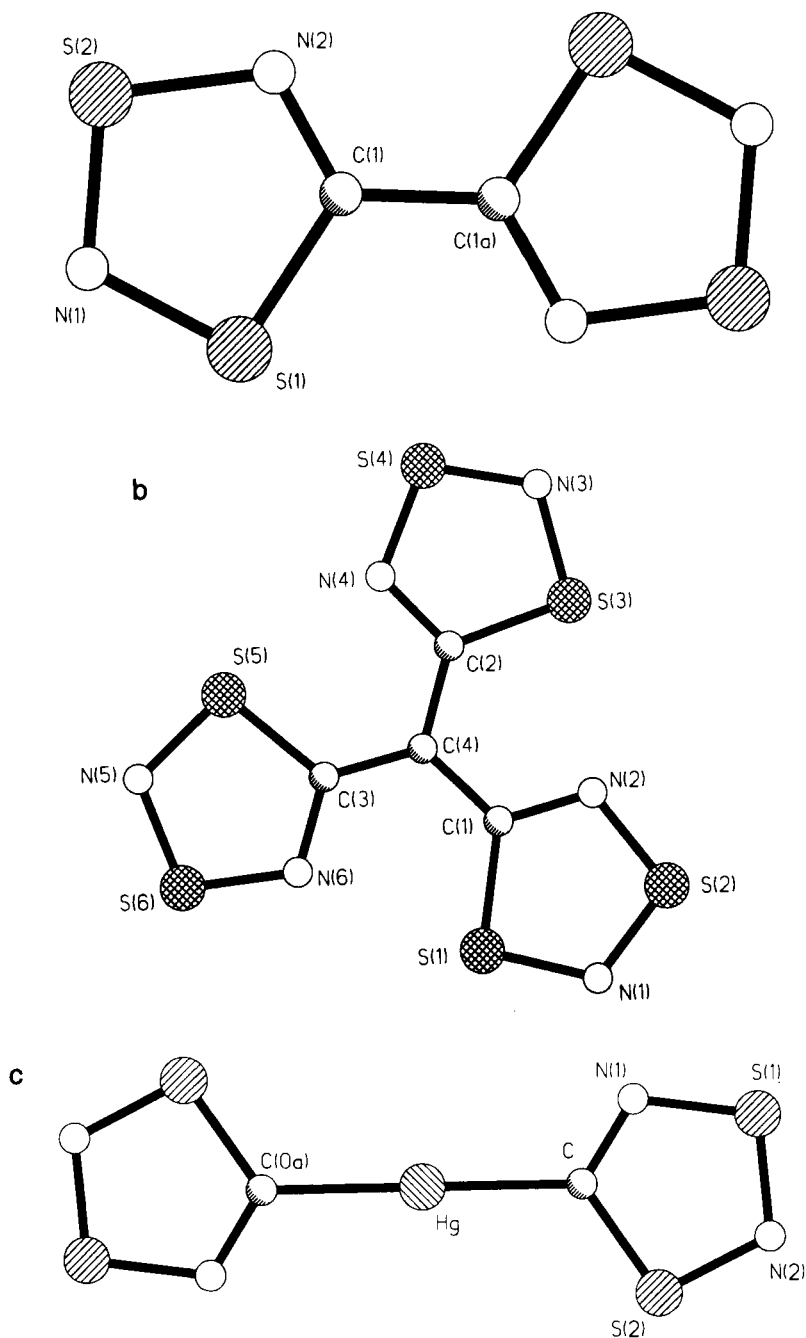


FIG. 25. Structures of the cations in (a) $[(\overline{\text{CNSNS}})_2][\text{AsF}_6]_2$, (b) $[\text{C}(\overline{\text{CNSNS}})_3][\text{AsF}_6]_2$, and (c) $[\text{Hg}(\overline{\text{CNSNS}})_2][\text{AsF}_6]_2$.

TABLE XV
HETEROCYCLIC BOND DISTANCES (Å) FOR MULTI-1,3,2,4-DITHIADIAZOLYLIUM SALTS

Compound	C—N(1)	N(1)—S(1)	S(1)—N(2)	N(2)—S(2)	S(2)—C	Reference
$[(\overline{\text{CNSNS}})_2][\text{AsF}_6]_2$	1.298	1.615(7)	1.600(8)	1.593(8)	1.718(8)	91CC369 93JCS(D)1499
$[\text{C}(\overline{\text{CNSNS}})_3][\text{AsF}_6]_2$	1.324(7)	1.595(5)	1.569(5)	1.619(5)	1.752(6)	92JCS(D)859
$[\text{Hg}(\overline{\text{CNSNS}})_2][\text{AsF}_6]_2$	1.29(2)	1.622(11)	1.590(10)	1.617(12)	1.734(11)	94CC29

to remove the final traces of soluble contaminant, increasing purity levels to >95%.)

E. X-RAY DIFFRACTION STUDIES OF MULTI-1,3,2,4-DITHIADIAZOLYL RADICALS

The greater thermal stability (and lower solubility) of these multiradicals (compared with monoradicals) has allowed several derivatives to be isolated in the solid state, e.g., **86**^{3·}, **87**^{2·}, and **89**^{2·}. However, of these only **87**^{2·} has been fully characterized by an X-ray crystal structure determination. Its structure (Fig. 26) is unique and shows a regular polymeric array of radicals held together in a head-to-tail fashion through spin-paired out-of-plane S . . . S interactions, and these are accompanied by other in-plane S . . . N interactions [91JCS(D)1099].

These out-of-plane interactions between radical centers are identical to those proposed, on theoretical grounds, to be responsible for the solution-state rearrangement of **3**[·] radicals (Section XXI.A.1); we will see later (Section XXIII.G.3) that this material undergoes an unprecedented mode or rearrangement in the solid state.

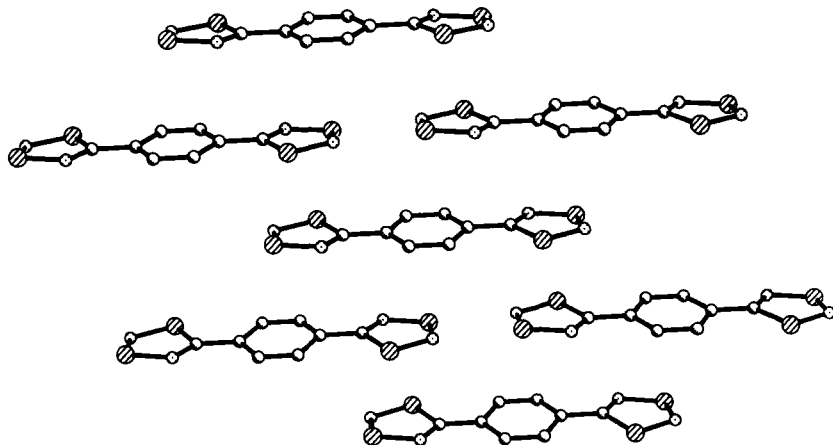
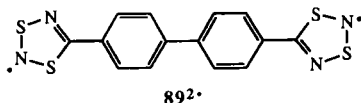


FIG. 26. Molecular packing of $[p\text{-C}_6\text{H}_4(\overline{\text{CNSNS}})_2]$.

F. PHYSICAL PROPERTIES OF MULTI-1,3,2,4-DITHIADIAZOLYL RADICALS

1. Electron Spin Resonance Spectra

The esr spectra of multi-1,3,2,4-dithiadiazolyl radicals have been examined extensively (93UP13). These radicals possess the typical 1 : 1 : 1 triplet ($g \sim 2.01$, $a_N \sim 1.1$ mT) associated with $3'$ radicals, plus spin-spin exchange bands at $a_N/2$ (comparable to those observed for multi-1,2,3,5-dithiadiazolyls; Section XXII.F.1). Perfluorinated radicals also exhibit secondary coupling to *ortho*-fluorine atoms ($a_F \sim 0.1$ mT) (93UP9). Electron spin resonance spectra for a series of these radicals (Fig. 27) have shown that the exchange process is complex and that simple through-bond coupling is not a satisfactory explanation. Extensive coupling occurs in $89^{2\cdot}$, in which the radical separation is largest, but little coupling is observed for $87^{2\cdot}$ or $85^{2\cdot}$.



The exchange process also appears to be temperature- and solvent-dependent, and an indirect exchange pathway—possibly mediated by solvent molecules—may explain the complex behavior of such systems.

2. Electronic Properties

Magnetic susceptibility measurements on powder samples of $87^{2\cdot}$ show a significant number (<16%) of unpaired spins per molecule, indicating many lattice defect sites (*cf.* crystalline samples of multi-1,2,3,5-dithiadiazolyl radicals, with <1%). However, more crystalline samples of this material showed a magnetic response consistent with <5% unpaired spins per molecule [93JCS(D)1421]. Similar magnetic responses were observed for $86^{3\cdot}$ and $89^{2\cdot}$, indicating that the radical centers are held together through spin-paired interactions. Pressed-pellet conductivities of $87^{2\cdot}$ and $89^{2\cdot}$ showed these materials to be insulators at room temperature (conductivity $<10^{-10}$ S/cm).

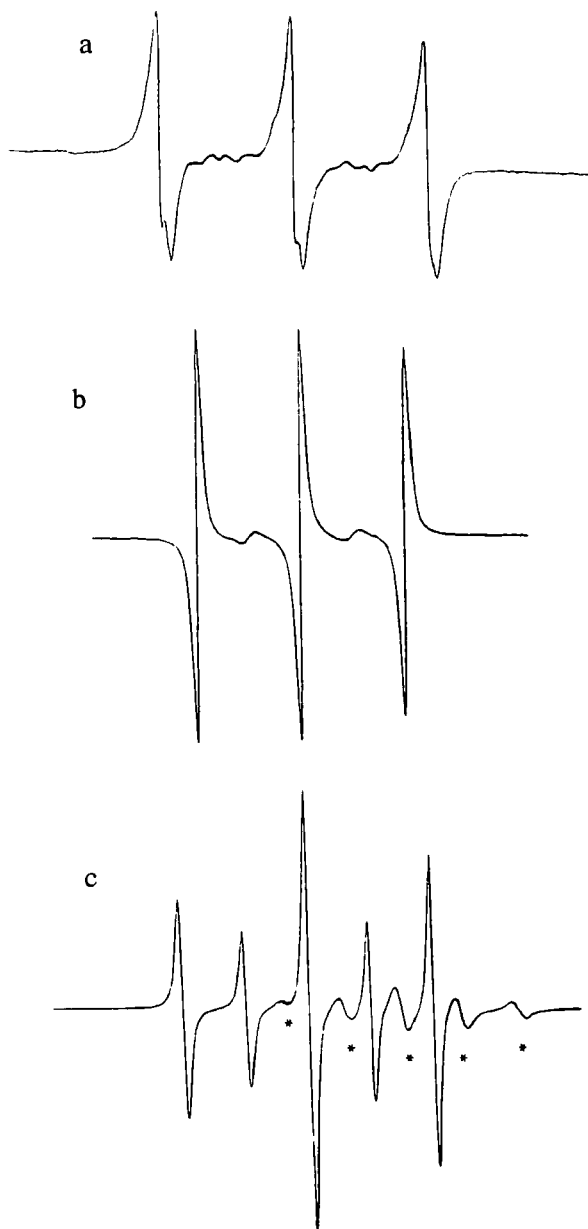
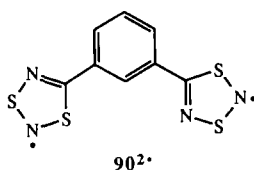


FIG. 27. Room-temperature esr spectra of some multi-1,3,2,4-dithiadiazolyl radicals: (a) $C(\overline{CNSNS})_3$, (b) $p\text{-C}_6\text{H}_4(\overline{CNSNS})_2$, and (c) $4,4'\text{-(}\overline{SNSNC}\text{)}_2\text{C}_6\text{H}_4\text{C}_6\text{H}_4(\overline{CNSNS})$. (Resonances marked with an asterisk may be attributable to the isomeric 1,2,3,5-dithiadiazolyl radical.)

G. REACTIVITY OF MULTI-1,3,2,4-DITHIADIAZOLYL RADICALS

1. *Oxidation*

Direct bromination of $90^{2\cdot}$ and $86^{3\cdot}$ led to the corresponding tribromide salts $[90][Br_3]_2$ and $[86][Br_3]_3$, which on warming in vacuo lost bromine to give the corresponding bromides, $[86]Br_3$, etc. (92TH1).

2. *Solution Rearrangement*

As found for 3^{\cdot} , these multiradicals undergo rearrangement in solution. Apart from $84^{+\cdot}$ and presumably $84^{2\cdot}$, which rearrange at room temperature, radicals such as $86^{3\cdot}$, $87^{2\cdot}$, and $89^{2\cdot}$ are all (in the absence of moisture in the solution) stable and undergo rearrangement only on photolysis or warming ($>60^\circ C$) (93UP13). However, the lack of exchange resonances at $a_N/2$ in the esr spectra indicate that this rearrangement may also be accompanied by some degree of decomposition (93UP13).

3. *Solid-State Rearrangement*

Although several multi-1,3,2,4-dithiadiazolyl radicals are indefinitely stable in the solid state (in the dark, or for several weeks under normal illumination) without significant degradation [92JCS(D)1277], many are unstable on heating ($120\text{--}300^\circ C$), undergoing a strongly exothermic decomposition ($\Delta H = 317 \pm 10$ kJ/mol for $87^{2\cdot}$). On closer examination, this process was found to be associated with a solid-state rearrangement to the isomeric multi-1,2,3,5-dithiadiazolyl radicals [92JCS(D)1277]. The high yields (typically $>75\%$) are exceptional for such a process. A comparison of the solid-state structure of $87^{2\cdot}$ (Section XXIII.E) and that proposed for the solution rearrangement of 3^{\cdot} shows that a similar process is likely to occur for both systems. It has been proposed [92JCS(D)1277] that all radicals undergoing such rearrangement processes must possess a head-to-tail arrangement of radicals analogous to that observed in $87^{2\cdot}$. X-Ray powder diffraction studies on $78^{2\cdot}$ prepared by (i) thermolysis of $87^{2\cdot}$

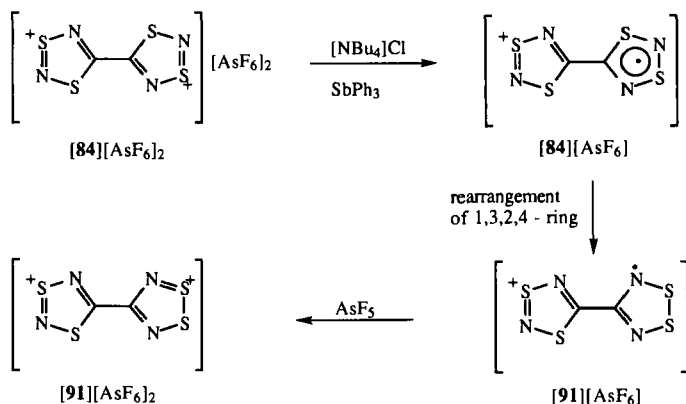
and (ii) standard synthetic techniques, show that they possess the same morphology; i.e., the same phase is observed for both materials. However, this may not necessarily be the case for all thermolysis products.

XXIV. Mixed 1,3,2,4-/1,2,3,5-Dithiadiazolylium Salts and Related Free Radicals

A. PREPARATION OF MIXED 1,3,2,4-/1,2,3,5-DITHIADIAZOLYLIUM SALTS

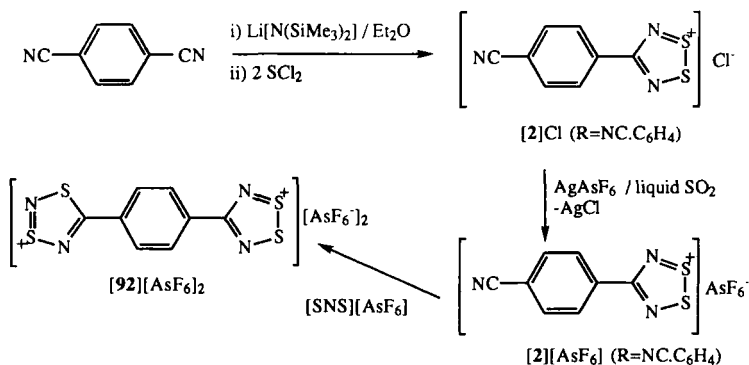
1. From Multi-1,3,2,4-dithiadiazolylium Salts

The first salts to contain both 1,3,2,4- and 1,2,3,5-dithiadiazolylium rings were reported in 1991, and were prepared via partial reduction, rearrangement and subsequent reoxidation of **[84]**[AsF₆]₂ [91CC369; 93JCS(D)1499]. However purification of **[91]**[AsF₆]₂ by fractional recrystallization led to low yields (39%).



2. By Sequential Heterocyclic Ring Synthesis

A high-yielding synthesis of a phenylene-bridged species, which avoids any rearrangement step, has recently been reported [92JCS(D)1499; 93JCS(D)1421]. This synthesis combines standard synthetic approaches for both 1,2,3,5- and 1,3,2,4-dithiadiazolylium rings, **[92]**[AsF₆]₂ being recovered in overall 63% yield for the three-step synthesis.



B. PHYSICAL AND CHEMICAL PROPERTIES

Cyclic voltammetry studies of $[92][\text{AsF}_6]_2$ show two reversible one-electron reductions at half-wave potentials typical of the constituent 1,2,3,5- and 1,3,2,4-dithiadiazolylium salts. ^1H nmr data for $[92][\text{AsF}_6]_2$ show four multiplet resonances (equivalent to four distinct phenylene protons), suggesting that there is some barrier to free rotation about the heterocyclic-phenylene bonds at room temperature. ^{13}C nmr data for $[91][\text{AsF}_6]_2$ show two resonances, typical of those for other dithiadiazolylium heterocyclic carbon atoms ($\delta = +190.0, +169.8$ ppm).

Reaction of $[92][\text{AsF}_6]_2$ with two equivalents of $[\text{NBu}_4]\text{Cl}$ yielded $[92]\text{Cl}_2$ in a fashion analogous to that for other multidithiadiazolylium salts (Section XXIII.B.2) [93JCS(D)1421].

C. X-RAY DIFFRACTION STUDIES OF MIXED 1,3,2,4-/1,2,3,5-DITHIADIAZOLYLIUM SALTS

The only structure determination to be reported to date is that of $[92][\text{AsF}_6]_2$, which was crystallized as a MeCN solvate. Its structure is shown in Figure 28.

Bond distances and angles are similar to those observed for the related phenyl- and phenylene-substituted compounds described previously (Sections V.A, XV, and XXII.C). The solvent molecule interacts weakly with the 1,2,3,5-dithiadiazolylium heterocyclic ring, but it does not appear to induce any significant structural perturbations. As with other 1,2,3,5- and 1,3,2,4-dithiadiazolylium salts, weak anion-cation interactions are seen between fluorine and both carbon and sulfur, but not between fluorine

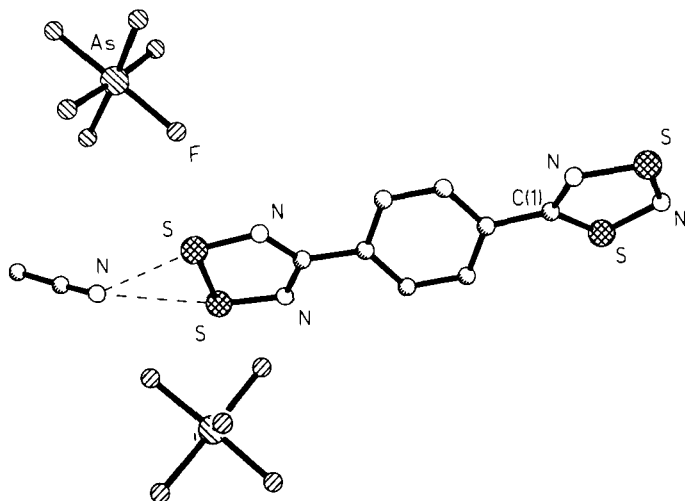


FIG. 28. Crystal structure of $[\overline{\text{S}}\overline{\text{N}}\overline{\text{S}}\overline{\text{N}}\overline{\text{C}}.\text{C}_6\text{H}_4.\overline{\text{C}}\overline{\text{N}}\overline{\text{S}}\overline{\text{S}}\overline{\text{N}}][\text{AsF}_6]_2.\text{MeCN}$.

and nitrogen; this is consistent with fractional negative charges at both fluorine and nitrogen atoms.

D. CHEMISTRY OF 1,3,2,4-DITHIADIAZOLYLIUM-1,2,3,5-DITHIADIAZOLYL RADICALS

1. Preparation

The different reduction potentials of the two heterocyclic rings means that the 1,2,3,5-dithiadiazolylum ring is reduced first and bears the unpaired electron while the 1,3,2,4-dithiadiazolylum ring remains cationic. Partial reduction of **[84]** $[\text{AsF}_6]_2$ [91CC369; 93JCS(D)1499] initially forms **84**⁺, which then undergoes rearrangement to **91**⁺. Attempts to isolate **[91]** $[\text{AsF}_6]$ on the preparative scale have been thwarted by difficulties of purification [93JCS(D)1499]. In contrast, **[92]**Cl can be prepared conveniently by reduction of **[92]**Cl₂ with half an equivalent of Ph₃Sb [93JCS(D)1421]. The salt **[92]** $[\text{AsF}_6]$ can also be prepared by reaction of **[92]** $[\text{AsF}_6]_2$ with **92** (93UP14). These compounds are stable with respect to (i) disproportionation and (ii) thermal or photochemical isomerization.

2. Electron Spin Resonance Spectra

The solution esr spectrum of $\mathbf{91}^{+\cdot}$ consists of a 1:2:3:2:1 pentet ($a_N = 0.4578$ mT) of 1:1:1 triplets ($a_N = 0.025$ mT) with a g -value of 2.0119. Secondary coupling to the $\bar{C}NSNS^+$ near-nitrogen indicates some degree of spin delocalization onto the second, predominantly cationic, ring [93JCS(D)1499]. Coupling to two equivalent nitrogen atoms and an exocyclic nitrogen implies that the two heterocyclic rings are either mutually perpendicular or freely rotating in solution at room temperature. In comparison, $\mathbf{92}^{+\cdot}$ shows only a 1:2:3:2:1 pentet ($g = 2.01$, $a_N = 0.5$ mT) consistent with localization of the unpaired electron on the 1,2,3,5-dithiadiazolyl radical, enhanced by the greater separation between heterocyclic rings [93JCS(D)1421].

3. Magnetism

Variable-temperature magnetic data have been reported for $[\mathbf{92}]\text{Cl}$. This salt exhibits $S = \frac{1}{2}$ paramagnetism at room temperature, with Curie-Weiss behavior ($\theta = -65\text{K}$) above 160K [93JCS(D)1421]. The slightly high effective magnetic moment $1.87 \mu_B$ observed for this material (*cf.* idealized $1.73 \mu_B$ for an $S = \frac{1}{2}$ paramagnet) can be attributed to lattice defects in which chloride anion absences are counterbalanced by the presence of diradical $\mathbf{92}^{2\cdot}$ units (see Section XXIII.F.2). Below 100K the best Curie-Weiss fit ($\theta = -11\text{K}$) to the observed magnetic data, is represented by a paramagnetic material with an effective magnetic moment of $2.6 \mu_B$. Such a change in magnetic response has been proposed to occur via a phase transition [93JCS(D)1421].

E. CHEMISTRY OF 1,2,3,5-/1,3,2,4-MULTIDITHIADIAZOLYL RADICALS

1. Preparation

These materials are prepared by complete reduction of the parent dication $[\mathbf{92}]\text{Cl}_2$ with Ph_3Sb [93JCS(D)1421]. Radical $\mathbf{92}^{2\cdot}$ is sparingly soluble in common organic solvents and is readily isolated, although exhaustive solvent extraction is sometimes required to remove final traces of organic impurities. In contrast, neither reduction of $[\mathbf{91}][\text{AsF}_6]_2$ or $[\mathbf{91}][\text{AsF}_6]$ nor further rearrangement of $\mathbf{84}^{2\cdot}$ has been reported.

2. Electronic Properties

The overlapping 1:2:3:2:1 pentet ($g = 2.01$, $a_N = 0.499$ mT) and 1:1:1 triplet ($g = 2.005$, $a_N = 1.101$ mT) esr spectra observed for solutions of $\mathbf{92}^{2\cdot}$ indicate that the radical centers possess noninteracting electrons. This is entirely consistent with the behavior of the radical cation $\mathbf{92}^{2+}$, which shows localization of its unpaired spin on the 1,2,3,5-dithiadiazolyl ring and no delocalization onto the 1,3,2,4-heterocycle [92JCS(D)1449; 93JCS(D)1421].

As for other multidithiadiazolyl radicals (Sections XXII.F and XXIII.F), $\mathbf{92}^{2\cdot}$ is essentially diamagnetic in the solid state with a residual paramagnetic response (estimated at $\sim 3\%$ unpaired spin per molecule) arising from lattice defect sites [93JCS(D)1421].

XXV. Conclusions

The development of CN_2S_2 -ring chemistry shows the value of seeking analogs of any system that does not appear to fit current rationalizations of structure, physical properties, or reactivities. It also illustrates the great value of new reagents (e.g., $[\text{SNS}]^+$, NSCl , and $\text{N}(\text{SCl})_2^+$).

Much of the work has gone in predictable directions: e.g., the search for isomeric and isoelectronic rings, the synthesis of multiring systems, and the synthesis of salts with electron-donor anions. Nevertheless, there have been several especially useful new developments; the use of silyl and ring-transfer reagents in heterocyclic synthesis; the search for compounds exhibiting novel electronic and magnetic properties including free-radical liquids; and the formation of metal complexes.

In the future we can anticipate further progress in the preparation and derivitisation of dithiadiazolyl compounds and their metal complexes; tailored to specific applications in the field of solid state chemistry and physics.

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The Reactivity of Tetrathia- and Tetraselenafulvalenes*

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I. Introduction and Scope	249
II. Reactivity of Tetrathiafulvalenes	251
A. General Survey	251
B. Reactivity at the Ring Atoms	251
1. Photochemical Reactions Involving No Other Species	251
2. Reactions with Electrophiles	252
3. Reactions with Nucleophiles	253
4. Reactions with Free Radicals	256
5. Reactions with Cyclic Transition States	256
C. Reactivity of Substituents	257
1. Fused Benzene Rings	257
2. C-Linked Substituents	258
3. N-Linked Substituents	266
4. S- and Se-Linked Substituents	266
5. Halo Groups	274
6. Metallo Groups	275
7. Fused Heterocyclic Rings	291
III. Reactivity of Tetraselenafulvalenes	292
A. General Survey	292
B. Reactivity at the Ring Atoms	292
C. Reactivity of Substituents	293
1. C-Linked Substituents	293
2. S- and Se-Linked Substituents	294
3. Metallo Groups	294
References	296

I. Introduction and Scope

Tetrachalcogenafulvalenes are the most widely used heterocyclic systems in the development of new organic molecular materials, especially those with unconventional electronic properties. It should be remembered

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that the first organic metal was the charge-transfer complex TTF–TCNQ (where TTF is tetrathiafulvalene and TCNQ is tetracyanoquinodimethane) and the first organic superconductor was (TMTSF)₂PF₆ (where TMTSF is tetramethyltetraselenafulvalene). An enormous amount of work has been carried out in this field over the last two decades; the interested reader is referred to some recent books [87MI1; 88MI1; 90MI1; 92MI1; 92MI2], review articles [87MI2; 88CBR781; 89MI1; 91CSR355; 91SCI(252)1501; 91SCI(252)1509; 92MI3; 93MI1; 94CSR41], and detailed conference proceedings (87MI3; 87MI4; 88MI2; 89MI2; 90MI2, 90MI3; 91MI1; 93MI2) to obtain a general overview of the state of the art in this area.

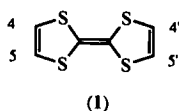
Moreover, the search for new materials incorporating the tetrachalcogenafulvalene moiety has led not only to the preparation of a considerable number of conducting organic crystals, but also to electroactive Langmuir–Blodgett films (91CSR355), compounds with interesting nonlinear-optical properties (93MI1), molecular sensors (92BSB555; 92JOC6403; 93JOC1359; 93MI1; 94CSR41), and “molecular shuttles,” (92SL923), among others that are undoubtedly of great interest in the emerging science of molecular electronics (91NJC209; 92MI4; 93MI3).

However, it should be borne in mind that as far as molecular materials are concerned, serendipity is still a nonnegligible factor in the search for compounds with interesting properties since the study of structure–activity relationships is in its infancy owing primarily to the subtle combination of structural and electronic factors that are often involved. As a consequence, advances in this area rely heavily on the success of chemists in the preparation of the newly sought after tetrachalcogenafulvalenes. It is, therefore, hardly surprising that a great deal of work has been devoted to the synthesis of these substances, a topic that has been covered in several excellent reviews [76S489; 85MI1; 86T1209; 87MI5; 87MI6; 92PS(67)277; 93MI4].

Although the synthesis of tetrachalcogenafulvalenes has been widely reviewed, there is no account in the literature dealing solely with the reactivity of tetrachalcogenafulvalenes. The purpose of this review is to fill this gap by providing the reader with an updated account of this subject, covering the literature from 1986 up to the beginning of 1994, although some references to previous work are also included where relevant. A description of the preparation of charge-transfer salts derived from tetrachalcogenafulvalenes and their physical and structural characterization is well beyond the scope of this review and, therefore, will not be undertaken. Thus, only reactions in which covalent bonds are formed or broken will be covered. To our knowledge, there are no reports describing the reactiv-

ity of tetratellurafulvalenes, so this review will deal with the chemical properties of tetrathia- (Section II) and tetraselenafulvalenes (Section III), although references are made to diselenadithiafulvalenes and vinylogous tetrathiafulvalenes where appropriate.

Throughout the review TTF stands for tetrathiafulvalene (1) itself, namely 2,2'-bi(1,3-dithiolylidene). For all tetrathiafulvalene derivatives, the adopted numbering scheme is shown alongside the formula.



II. Reactivity of Tetrathiafulvalenes

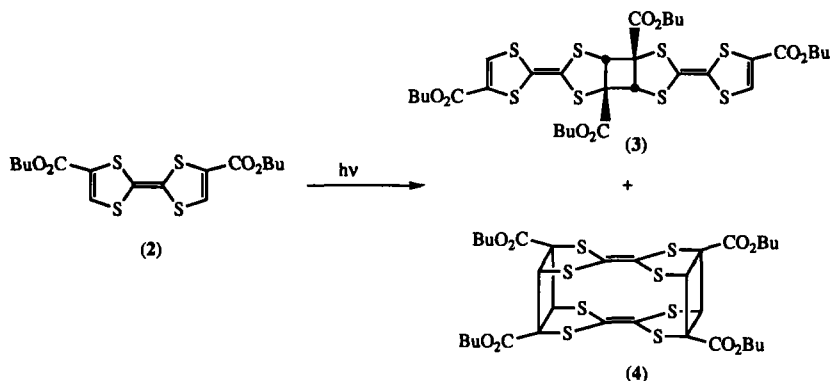
A. GENERAL SURVEY

The chemistry of TTF derivatives has only recently undergone major developments. The lithiation of tetrathiafulvalenes (Section II.B.3) undoubtedly constitutes the most significant development, because the metallated species formed give rise to a wealth of new derivatives (Section II.C.6), many of which bear functional groups that are amenable to further synthetic elaboration (Section II.C). In contrast, very few examples of the reactions of tetrathiafulvalenes with either electrophiles (Section II.B.2) or radicals (Section II.B.4) are known, and reports on $[2 + 2]$ - and $[4 + 2]$ -cycloadditions of TTF are scarce (Sections II.B.1 and II.B.5). Thus, the chemistry of tetrathiafulvalenes is dominated by the introduction and modification of substituents, whereas investigation of the reactivity of the ring atoms is relatively undeveloped.

B. REACTIVITY AT THE RING ATOMS

1. Photochemical Reactions Involving No Other Species

Compound **2** undergoes a $[2 + 2]$ -photochemical dimerization in the solid state to afford a mixture of the cyclobutane derivative **3** and the cage compound **4** (86ZOR416; 90BCJ2368) (Scheme 1). Interestingly, the trans isomer of **2** does not undergo such dimerization, but is converted to **2** on exposure to sunlight in benzene solution.



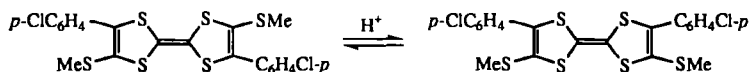
SCHEME 1

2. Reactions with Electrophiles

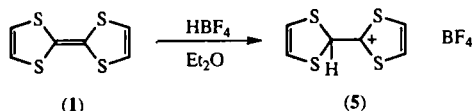
Despite the π -electron-rich character of tetrathiafulvalenes, very few reactions with electrophilic reagents have been described, since they usually lead to oxidation rather than to substitution and/or addition. The only known products of attack on sulfur are the *S*-oxides [78JOC4394; 79JCS(P2)862] and a formally *S*-alkylated derivative produced in the reaction of TTF⁺ with a free radical, rather than by electrophilic attack (Section II.B.4).

On the other hand, protonation of the central C=C bond by strong acids has been cited to explain the easy *cis*/*trans* isomerization observed with some 4,4'(5')-disubstituted tetrathiafulvalenes (84JOC564; 87JOC-1610) (Scheme 2).

For some tetrathiafulvalene cage products (88AG(E)1377; 92JOC2374) and TTF-cryptands (93JOC1359) it has been possible to characterize spectroscopically (by UV and ¹H and ¹³C-NMR) the resulting dithiolium cations, which are reversibly deprotonated on treatment with NH₃ or NEt₃. Moreover, **5** can be isolated quantitatively as a stable solid (Scheme 3), whose structure has been confirmed by X-ray diffraction (93CC944). This compound provides the first evidence of protic acid doping of tetrathiafulvalenes (94MI1).



SCHEME 2



SCHEME 3

Similarly, protonation of 1,4-dithiafulvenes, such as **6**, constitutes the key step in their isomerization to spiro compounds **7** (93TL2131) (Scheme 4), a process that can also be initiated by anodic oxidation (94TL1991) or electron-impact ionization (94OMS571).

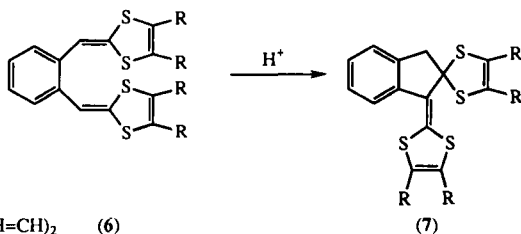
3. Reactions with Nucleophiles

a. *Attack at Carbon.* Not surprisingly, tetrathiafulvalenes are very unreactive towards attack by nucleophilic reagents. In fact, the only recorded examples are "transdithiolation" reactions, where benzene-1,2-dithiolates attack tetrathiafulvalenes bearing several electron-withdrawing groups such as COOMe or CN (78JOC416; 81TL2035). Nevertheless, BuLi does attack TTF itself, although only to a small extent (92MI5) (cf. Section III.B).

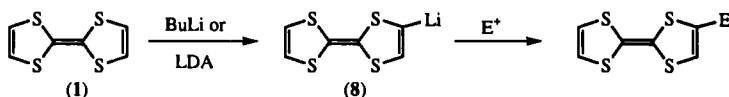
b. Attack at Hydrogen Attached to Carbon

i. *Substrates, Metallating Agents, and Solvents.* The acidity of the hydrogen atoms of tetrathiafulvalene (**1**) was first recognized by Green who, in a series of seminal papers [77CC161; 78ANY(313)361; 78CC832; 79JOC1476], described the preparation of tetrathiafulvalenyllithium (**8**) (Scheme 5) by the reaction of TTF with BuLi or LDA. Green demonstrated the versatility of this species by preparing a number of substituted tetrathiafulvalene derivatives through the reaction of **8** with carbon electrophiles.

Since then, other tetrathiafulvalene derivatives have been lithiated, the majority of which are methyl-substituted [**9** (79JOC1476; 92BSB741),

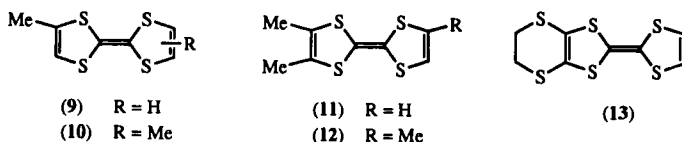


SCHEME 4



SCHEME 5

10 [79JOC1476; 92BSB137; 92BSB741; 93PS(75)175], **11** (92BSF29; 93OM797), **12** [92BSB741; 93OM797; 93PS(75)175], and ethylenedithiotetrathiafulvalene (EDT-TTF **13**) [91ZN(B)1269; 93MI5]. Tetrathiafulvalene derivatives bearing other substituents have only seldom been metallated and reference will be made to them where appropriate.

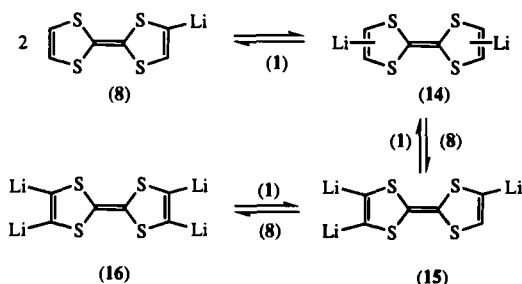


Tetrathiafulvalene and simple derivatives thereof have been routinely lithiated with BuLi or LDA in either Et₂O or THF. Although all of these systems seem to work well, LDA/Et₂O has proved to be the most satisfactory in the author's laboratory. Lithiation of **13**, however, has usually been carried out with LDA/THF [91ZN(B)1269; 93MI5].

Only seldom have other lithiating agents been used; these are MeLi (91CC92), LiHMDS (91CC92) and PhLi (89S207; 91CC92). There is also one report in the literature (89ZOR1456) describing the use of BuMgBr in THF as the metallating agent.

When tetralithiation of **1** is required, LDA/THF is the best combination to use, although PhLi/THF (89S207) and LDA/Et₂O (91S263) have also been employed. Some examples showing the advantages of LDA over BuLi in this reaction have been reported (86CL1861).

ii. Mono- versus Multilithiated Tetrathiafulvalenes. Monolithiated TTF-Li is a very reactive species, even at -70°C (the temperature at which it is usually generated and made to react with different electrophiles), but it undergoes disproportionation to give multilithiated species at higher temperatures (79JOC1476) (Scheme 6). Indeed, when using one equivalent of LDA, even at -70°C, the formation of small quantities of disubstituted products cannot be avoided [79JOC1476; 86H(24)1145; 91S263; 92T3983; 93JCS(P1)1403]. This problem is more troublesome when alkyl groups, such as methyl or ethyl, are introduced since the mono- and dialkylated derivatives, as well as unreacted **1**, have quite similar properties, thus making their purification difficult (79JOC1476; 92BSB137). In some instances, not only disubstituted but also tri- and



SCHEME 6

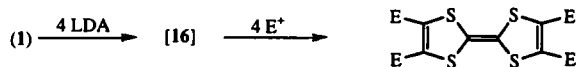
tetrasubstituted tetrathiafulvalenes have been obtained when using one equivalent of metallating agent (91CC92).

With two equivalents of LDA, **14** is formed in preference to the 4,5-dilithiated isomer, as determined from product distribution obtained by quenching the reaction mixture with different electrophilic reagents [78ANY(313)361; 79JOC1476; 85TL2783].

Tetalithiation of **1** was first reported (85TL2783) in 1985, and since then this method has been widely used to synthesize tetrasubstituted tetrathiafulvalenes [85TL2783; 86CL1861; 87CL2265; 87JOC3444; 87MI7; 87N(L)(329)39; 87PAC999; 88MI3; 88MI4; 88MI5; 89CC169; 89S207; 91CR(II)(313)1395; 91S263; 91TL2741; 92PS(67)367; 93JOC6480; 93MI6]. (Scheme 7).

Whether **16** is really formed or whether the reaction proceeds by subsequent lithiation-substitution steps is uncertain, but mono-, di-, and trisubstituted tetrathiafulvalenes are common side products of this reaction [91CR(II)(313)1395; 91TL2741; 93JOC6480; 93MI6] as is unreacted TTF (89S207; 91S263), which indicates that the equilibrium depicted in Scheme 6 is still present even when the molar ratio of metallating agent to TTF is 4:1. On the other hand, it has recently been claimed (93JOC6480; 93MI6) that using ten equivalents of LDA, followed by treatment of the reaction mixture with sulfur and then excess methyl iodide, leads to tetraakis(methylthio)tetrathiafulvalene, to the exclusion of its di- and trisubstituted analogs.

Analogously, EDT-TFF **13** has given rise to its dilithio derivative by treatment with two equivalents of LDA [91ZN(B)1269].



SCHEME 7

iii. **Substituent Effects.** With regard to substituted tetrathiafulvalenes, Green showed (79JOC1476) that electron-donating groups, such as methyl groups, direct lithiation to the unsubstituted ring, whereas electron-withdrawing groups, such as ethoxycarbonyl groups, increase the acidity of the adjacent protons, thus giving rise to 4,5-disubstituted derivatives (Scheme 8).

These directing effects, together with the lithiation–substitution step-wise mechanism mentioned previously, are thought to account for the appearance of 4,5-disubstituted products when electron-withdrawing groups (EWG), such as halogeno (91CC92; 91S263) or alkylthio [93JCS(P1)1403] groups, are introduced into the TTF core (Scheme 9).

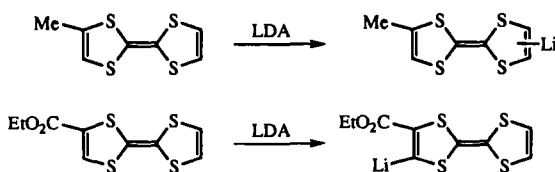
4,4'(5')-Dimethyltetrathiafulvalene (**10**) was reported (79JOC1476) not to react with LDA at -70°C , with lithiation being observed at temperatures as high as 25°C . However, this claim was later shown to be erroneous, since **10** has been lithiated at low temperatures (92BSB137; 92BSB741), as has its 4,5-isomer (**11**) (92BSF29; 93OM797). Moreover, trimethyltetrathiafulvalene (**12**) (92BSB741; 93OM797) and 4,5-ethylenedithio-4'-methyltetrathiafulvalene (93S509) have also been lithiated at low temperatures. These observations are in accord with a recent report indicating the small effect of a methyl group attached to the TTF nucleus on the pK_a values of the remaining ring protons [93JCS(P1)1403].

4. Reactions with Free Radicals

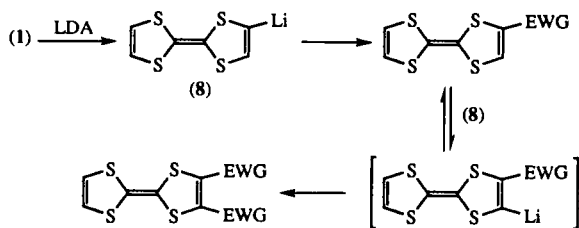
The reactivity of tetrathiafulvalenes toward free radicals has been little studied. Nevertheless, a recent report has shown that **1** can act as a catalyst for radical-polar crossover reactions (93CC295) (Scheme 10). In fact, compound **17** has been isolated (cf. Section II.B.2) and its reactions with nucleophiles result in the displacement of the TTF moiety.

5. Reactions with Cyclic Transition States

Some cycloaddition reactions of tetrathiafulvalene have recently been described (cf. Section II.B.1). For example, reaction of **1** with compounds



SCHEME 8



SCHEME 9

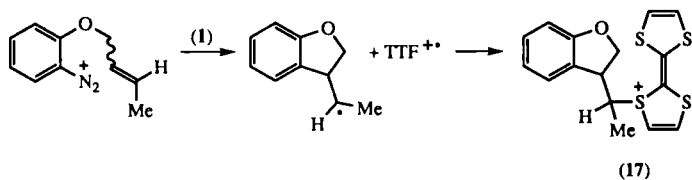
18 gives rise to **20** [91AG(E)1127] (Scheme 11). The proposed mechanism involves a [2 + 2]-cycloaddition between the C(2)—C(2') π -bond of **1** and the alkyne to generate **19**, which then opens to give **20**. The presence of the dicyanomethylene group appears to be important, since other activated alkynes fail to give this reaction.

Khodorkovsky *et al.* have shown that TTF itself (as well as some 4,5-disubstituted derivatives) acts as a dienophile in hetero-Diels–Alder reactions. Thus, treatment of **1** with **21** affords **22** in 45% yield (92S1071; 93MI7) (Scheme 12). Compound **22** is a good starting material for the preparation of new tetrathiafulvalenes, such as **23** and **24**. Moreover, the Diels–Alder reaction has been shown to be reversible at higher temperatures.

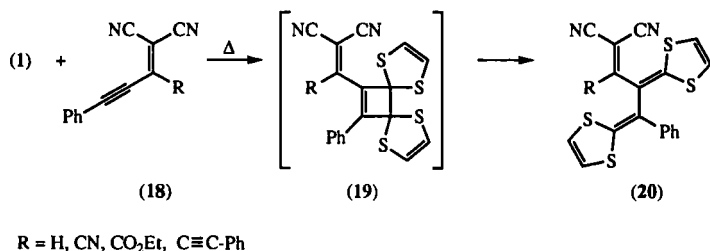
C. REACTIVITY OF SUBSTITUENTS

1. Fused Benzene Rings

There are no reports of aromatic substitution reactions on benzo- or dibenzotetrathiafulvalenes. With regard to the reactivity of the substituents on the benzene ring(s), the main examples involve 1,3-dithiol-2-ones and 1,3-dithiole-2-thiones. The former afford octakis(alkylthio)dibenzotetrathiafulvalenes **25** through basic ring opening and subsequent alkylation

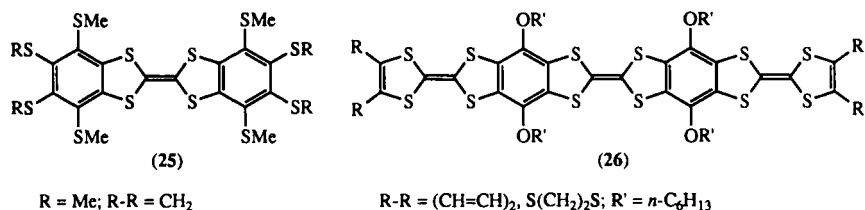


SCHEME 10



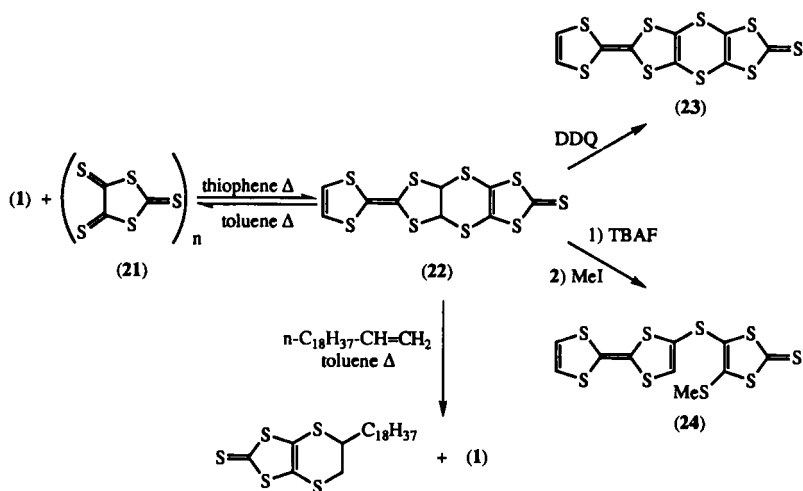
SCHEME 11

(90T1553; 91TL479), while the latter give rise to tristetrafulvalenes, such as **26**, when subjected to phosphite coupling (90CC1624; 93MI8).



2. C-Linked Substituents

a. Alkyl and Substituted Alkyl Groups. Reactions of the alkyl groups on simple alkyl-substituted tetrathiafulvalenes have not been reported to



SCHEME 12

date. There are, however, some reactions that have been carried out on substituted alkyl groups and these are discussed in the following sections.

i. Hydroxymethyl Groups. Compound **27** has been alkylated with alkyl iodides (94S489) and alkyl bromides (93MM4094), and its reactions with acyl halides afford the corresponding esters in good yields (94S489) (Scheme 13).

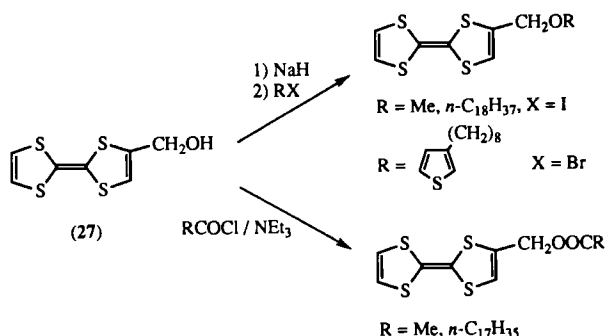
Tetraalcohol **28** has been dehydrated to **29** in 92% yield (88MI3) (Scheme 14).

ii. Other Substituted Alkyl Groups. Ethynylalkyl-substituted **13** has been subjected to Cadiot–Chodkiewicz coupling to give EDT–TTF-containing diynes (92TL973). ω -Carboxyalkyltetrathiafulvalenes have been made to react with amino esters and amino acids to give the corresponding amides, which were tested for Langmuir–Blodgett film formation (91MI2). Fanghanel and co-workers have disclosed that heating of the arylalkyl derivative **30** (either as the *cis* or the *trans* isomer, or a mixture thereof) results in dehydrogenation to give *trans*-**31** (Scheme 15). Other dihydrophenanthrenotetrathiafulvalenes behave similarly (93JPR599).

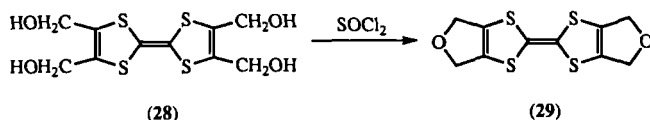
b. Aryl Groups. *p*-Acetoxyphenyl derivatives of **1**, **11**, and **12** have been treated with hydrazine to give the corresponding phenols (89MI3; 93BSB615), some of which have been reacted with poly(*p*-chloromethylstyrene) and related copolymers with a view to studying new microlithographic resins (89MI3).

Pyridine coupling of polymers **32** affords the conjugatively connected polymeric tetrathiafulvalenes **33**, where $n > m$ (Scheme 16) (89JPR826).

c. Formyl and Acyl Groups. The formyl group is one of the most synthetically useful groups in TTF chemistry since many standard transformations can be carried out with it, which is not the case for the majority



SCHEME 13



SCHEME 14

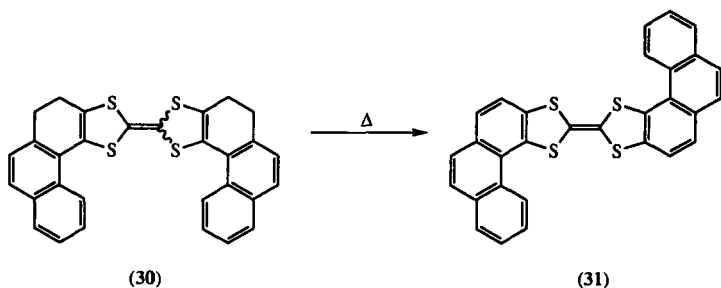
of other substituents on the TTF core. Thus, formyltetrathiafulvalene (**34**) (94S489) and compounds **35** (92TL2685) and **36** (89CC1520; 92T3081) are reduced by sodium borohydride to give the corresponding mono-, di-, and tetraalcohols, respectively, in excellent yields (Scheme 17).

Compound **34** has been subjected to reductive amination, giving rise to primary (**39**) and secondary (**40**) aminomethyl derivatives (92T3983), whose mass spectral behavior has been reported (93RCM587). Compounds **41** (93MI9), **42**, and **43** (93CL1361) have been prepared and some of their magnetic properties studies (Scheme 18).

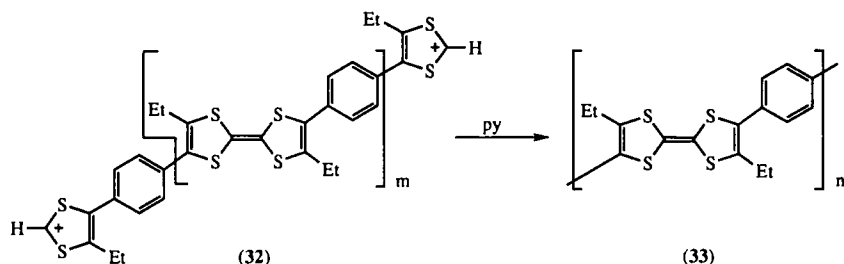
Treatment of **36** with hydrazine affords **44** (83CC405; 92T3081) (Scheme 19), and the reaction of the 4,4'-bis(diethylacetal) of **36** with phosphodihydrazides yields 26-membered macrocycles incorporating two TTF moieties (90TL6343).

The most studied reactions of formyltetrathiafulvalenes are of the Wittig type, mainly involving triphenylphosphoranylidene derivatives, although the use of phosphin oxides has been reported (91MI3). Using the Wittig reaction, compounds **45** (78CC832), **46** (89MI4), **47** (93CC417), **48** (93JCS(P1)1711; 93MI10), **49** (91MI3), **51** (94S489), **52** (94S489), and **53** (93TL7475) have been prepared from **34**, as has **50** (94S489) by a Knoevenagel reaction (Scheme 20).

Other Wittig reactions of **34** with bis- (92MI6; 92MI7) and trisphosphoranes (93JA3752) have also been carried out (Scheme 21). Compound **54**



SCHEME 15



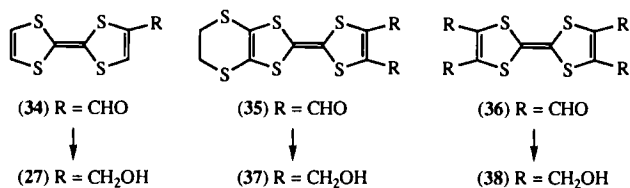
SCHEME 16

has given rise to **55** (93MI5), **56**, and **57** (94UP1) (Scheme 22), and a mass spectrometric study of **56** and **57** has been reported (93RCM815). Similarly, aldehydes **58**, prepared from **53** by Vilsmeier reaction, afford compounds **59** (93TL7475) (Scheme 23).

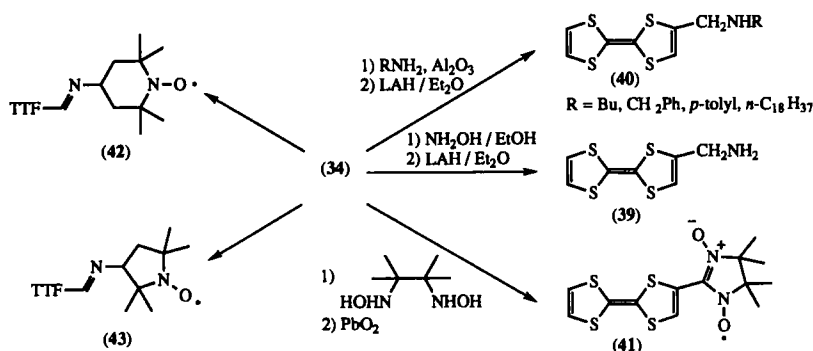
Gorgues and co-workers have studied the Wittig reactions of 4,5-diformyltetrathiafulvalene (**60**) and its 4',5'-dihydro analog, with a view to preparing new electron donors with extended conjugation, such as **61** (91MI4) (Scheme 24).

A variety of tetraolefination reactions have been carried out on **36** using stabilized and nonstabilized ylides, as well as Wittig (Horner) reagents derived from 1,3-dithioles (83CC405; 91MI4; 92T3081) (Scheme 25). This methodology has also been extended to vinylogous TTF derivatives, such as **62** (93TL4005) (Scheme 26).

The study of the chemistry of acyl groups other than formyl is much less developed. Acetyltetrathiafulvalene (**63**) has been subjected to crossed aldol condensations with acetylferrocene and (acetophenone) $\text{Cr}(\text{CO})_3$ [92JOM(429)335]. Some Wittig reactions of **63** have been reported (93TL7475), as well as a few reactions of ketone **64** (90CC816) (Scheme 27).



SCHEME 17



SCHEME 18

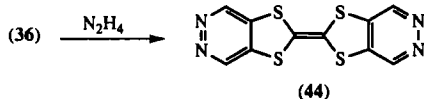
d. *Carboxy and Related Groups.* Reactions under this heading are classified into three subheadings: interconversion of carboxylic acid derivatives, reduction reactions, and removal of the COOH or COOR group(s).

i. *Interconversion of Carboxylic Acid Derivatives.* Acid **65** has been converted to acid chloride **66** (84MI1) and to esters **67** (R = Et, *n*-hexyl, *n*-octyl) (90CC816), **68** (*n* = 8, 11, 12, 16) (94L549), and **69** (91CPB1897). The latter has found use as an electrophore for precolumn labeling of amines in HPLC (Scheme 28).

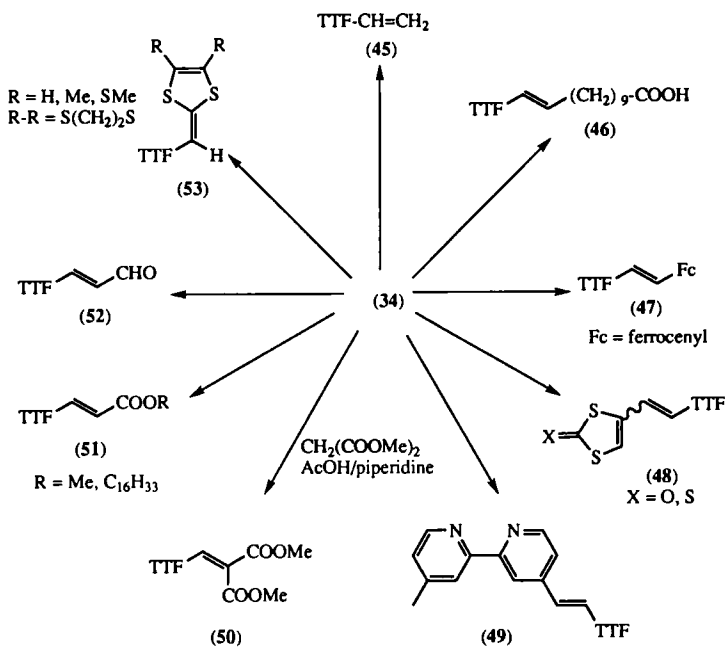
A different approach to the synthesis of tetrathiafulvalenecarboxylic acid esters involves alkylation of the corresponding cesium salts with alkyl halides. In this way, the methyl ester of **65** (92BSB741) and the benzyl esters of **70** and **71** have been prepared (92MI8) (Scheme 29). These cesium salts have also been made to react with poly(*p*-chloromethylstyrene) and related copolymers (89MI5; 92MI8).

In a similar way, diester **2** (cis + trans) has been prepared from diacid **72** (86ZOR416) (Scheme 30).

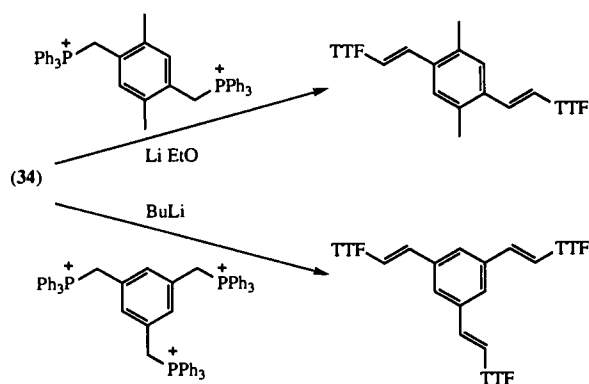
As expected, simple methyl esters of tetrathiafulvalenecarboxylic acids afford, upon basic hydrolysis, the free acids (86ZOR2372; 92BSB741). This procedure has been applied to the synthesis of molecules containing two TTF moieties (89ZOR1456; 93JOC1355) (Scheme 31). A number of



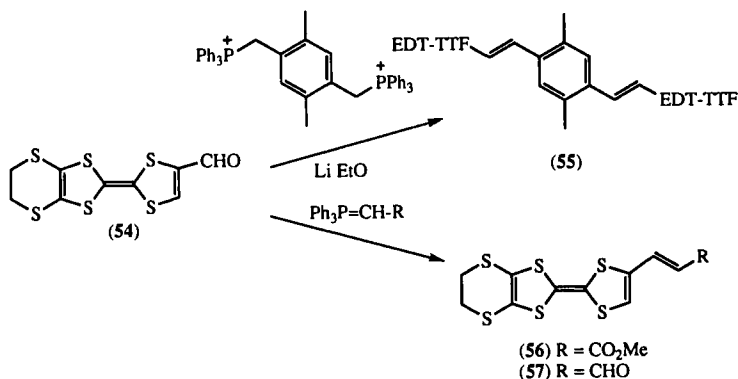
SCHEME 19



SCHEME 20



SCHEME 21

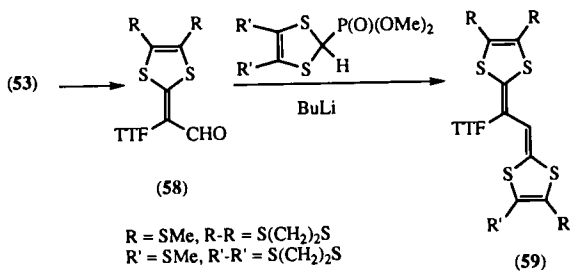


SCHEME 22

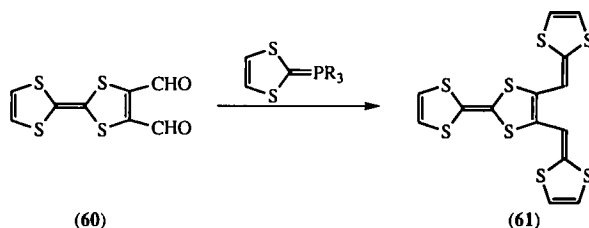
transesterification reactions have also been reported (86ZOR416; 89ZOR1456).

Acid chloride **66** reacts with sodium azide to afford **75** (84MI1), and with alcohols to afford esters **67** (R = *n*-hexyl, *n*-octyl) (90CC816), **76** (92JOC4859), and **77** (91MI5) (Scheme 32). A TTF-containing siloxane polymer has been prepared in a similar way and tested as an electron-transfer mediator in glucose oxidase-based amperometric biosensors (92HAC303). The dichloride of acid **72** has also been transformed to the corresponding dimethyl ester (92BSB741).

ii. Reduction Reactions. The reduction of carboxylic acid groups in derivatives of TTF was considered a puzzling problem until recently (76JOC1412; 76JOC2855). This problem has now been overcome and compounds **78** and **79** are easily reduced to **27** and **80**, respectively (93MI10).



SCHEME 23

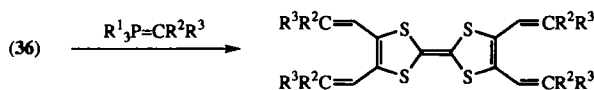


SCHEME 24

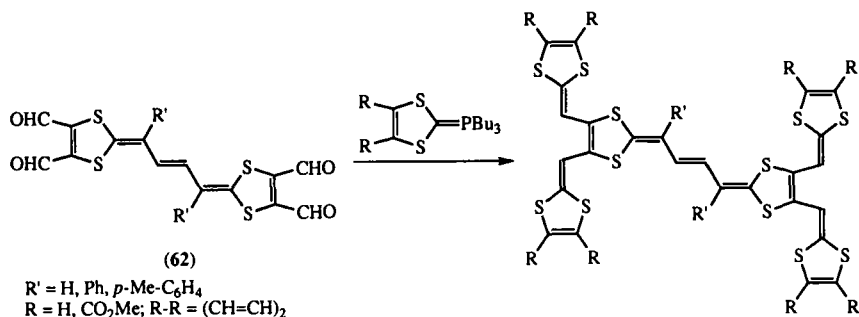
Similarly, **81** is reduced to **82** (93MI11), and selective reductions on **83** have been reported (92TL2685; 93MI11) (Scheme 33).

iii. Removal of the COOH or COOR Group(s). Decarboxylation of tetrathiafulvalenecarboxylic acids is not widely used, although some examples are known (93JOC1355). Indeed, this method allowed the synthesis of mono- and diiodotetrathiafulvalenes **85** and **86** (89ZOR1456) (Scheme 34).

On the other hand, decarbomethoxylation reactions have found widespread use in the synthesis of new tetrathiafulvalenes, since the corresponding methoxycarbonyl-containing tetrathiafulvalenes are often easier to prepare than the unsubstituted compounds. The decarbomethoxylation reaction, which is performed using lithium bromide in HMPA, has been carried out on (a) monoesters [91ZN(B)1730; 92TL2685]; (b) diesters, with a view to obtaining monodecarbomethoxylated (88MI6; 93MI11) or completely decarbomethoxylated derivatives (88MI6; 88MI7; 89CS123; 92CC1408; 93CC949; 93CL445; 93MI12; 93MI13; 94CC459); (c) tetraesters (89ZOR1456); and (d) vinylogous derivatives of tetrathia-, tetraselena-, or diselenadithia-fulvalenes with acyclic (88JOC3529; 89CM535; 89TL5289; 91JOC2720), carbocyclic (89CM535), and heterocyclic spacers (92JA5035; 93CC1617). The failure of this reaction has been reported in one case (93BCJ2330).



SCHEME 25



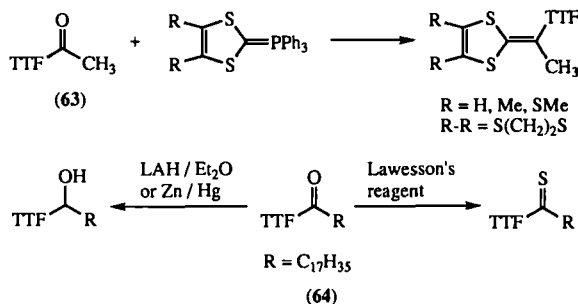
SCHEME 26

3. *N*-Linked Substituents

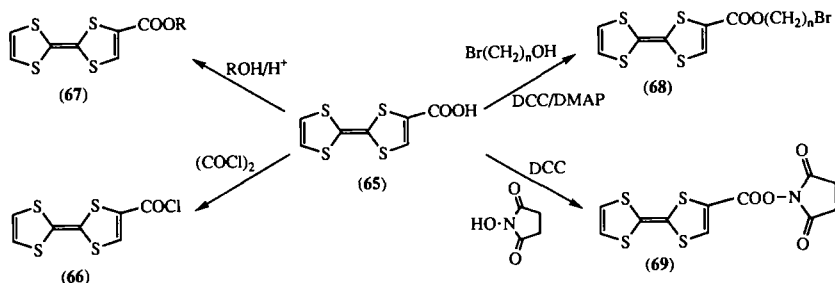
Aminotetrathiafulvalenes are, as yet, unknown and isocyanates are the only *N*-linked substituents of synthetic use. 4,4'(5')-Diisocyanatotetrathiafulvalene reacts with diols to afford polycarbamates (76JOC1412), whereas the reaction of **75** with alcohols (84MI1) has been explored in the search for novel D- σ -A materials (91SL301).

4. *S*- and *Se*-Linked Substituents

a. *Reactions Involving C—S (Se) Bonds.* Several stable derivatives with the general formula $\text{TTF}(\text{XR})_n$ ($n = 1-4$, $\text{X} = \text{S}, \text{Se}$) have been used in the preparation of alkylthio(seleno)tetrathiafulvalenes, via the generation of tetrathiafulvalenechalcogenolate anions and subsequent trapping with alkylating agents. Reactions in which the corresponding



SCHEME 27



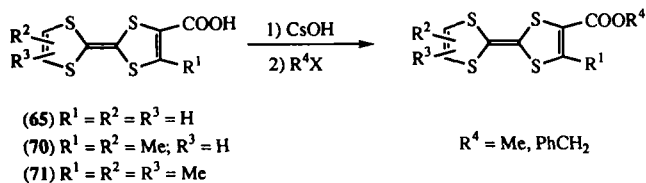
SCHEME 28

chalcogenolate anions are prepared from tetrathiafulvalenes by the sequence lithiation, reaction with elemental chalcogen, then quenching with electrophilic reagents will be treated separately (Section II.C.6.b).

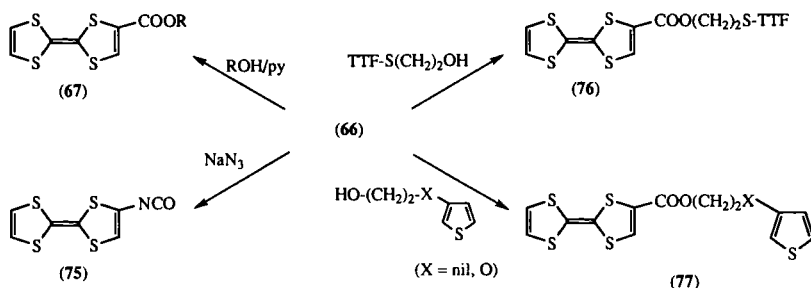
Benzoylthio derivatives, such as **87** and **88**, are synthetically interesting. Compound **87** is a shelf-stable equivalent of TTF—S[−] anion since, upon treatment with base, it affords sodium tetrathiafulvalenethiolate, which reacts with alkyl and acyl halides to give the corresponding derivatives (92JOC4859; 93CC417). Compound **88** undergoes analogous reactions [85ZOR1582; 91JCS(P2)1963] (Scheme 35).

4-Acetoxybenzylthio derivatives have also found use in the synthesis of new tetrathiafulvalenes owing to the easy cleavage of the S—benzyl bond. Compound **89** gives rise to the tetrathiafulvalenetetrathiolate anion (92TL3923), whereas other 4,5-disubstituted derivatives allow the preparation of unsymmetric tetrathiafulvalenes (92TL3923), some of which bear 1,3-dithiol-2-one groups, which are amenable to further synthetic transformations (92CL2321; 94CC459) (Scheme 36).

Tetrathiafulvalene-fused 1,3-dithiol-2-ones can either undergo standard phosphite coupling to afford new products containing two tetrathiafulvalene moieties (92CL2321; 93MI7; 94CC459) or can be cleaved by base to



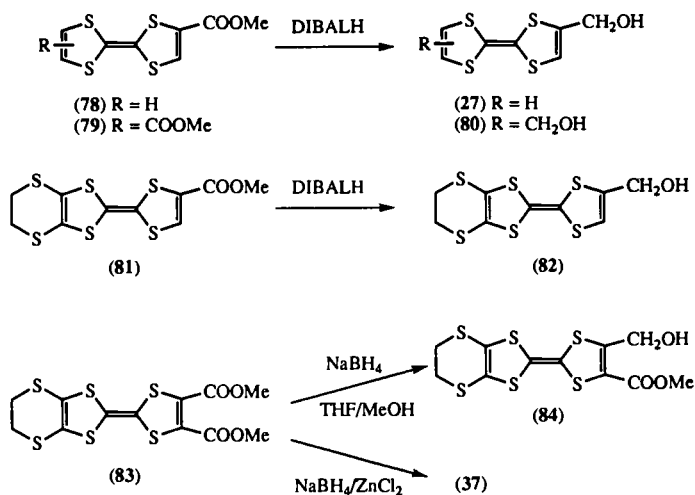
SCHEME 29



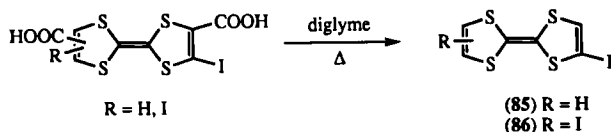
SCHEME 32

(Scheme 39). In contrast, the sulfur analog of **92** is surprisingly unreactive under identical conditions.

Tetrathiafulvalenes containing two alkylthio groups can be prepared analogously from diprotected compounds **93** (91MI6; 91TL2737) (Scheme 40), and some examples describing the synthesis of bis(alkylseleno)tetrathiafulvalenes (91TL2737) and bis(alkylthio) derivatives of diselenadithiafulvalenes (91TL2737) and selenatrithiafulvalenes (93MI14) have been reported.



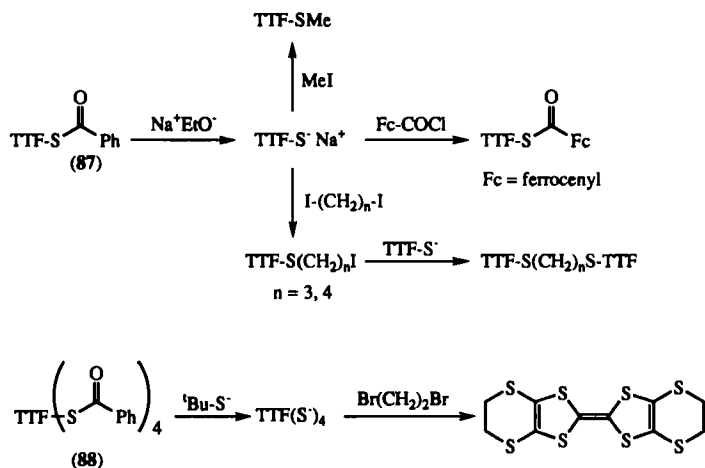
SCHEME 33



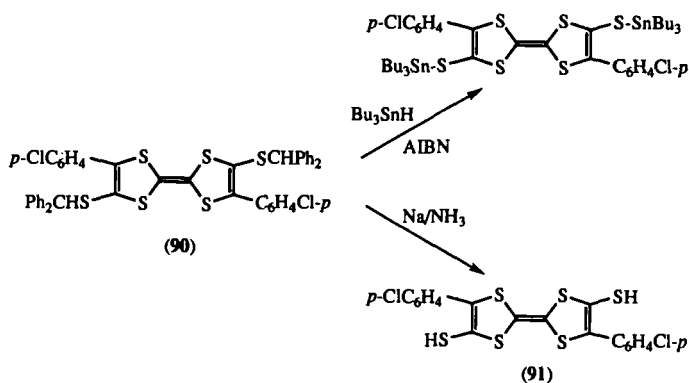
SCHEME 34

Fluoride ion-induced formation of bis- and tetrakis(vinylthio)tetrathiafulvalenes has been reported when 1,2-dibromoethane is used as the alkylating agent or when an ethylenedithio bridge is present in the starting material (91TL2737).

Tetrakis(alkylchalcogeno)tetrathiafulvalenes can also be prepared from **94** (87MI7). The synthesis of **95** takes advantage of the slower rate of deblocking of the SEM groups by fluoride ions as compared to that of the subsequent alkylation of the newly generated selenolate anion, thus disfavoring the appearance of polymeric by-products, which were the only ones obtained using previous approaches. However, the reaction failed with the analogous tetratellurolate species, possibly due to dehalogenation of the dibromoalkanes by the tetratellurolate species themselves (Scheme 41).



SCHEME 35



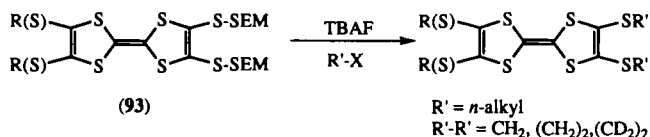
SCHEME 38

b. *Other Reactions.* Alkylthio substituents bearing different functional groups have been subjected to classical transformations. In this regard, the chemistry of **96** has been widely explored since it is a most versatile compound for the synthesis of monosubstituted tetrathiafulvalenes with side-chain functionality. Compounds **97** [91CC1638; 93JCS(P1)1403], **98** ($\text{R} = \text{Ph}$, $\text{CH}_2\text{CH}_2\text{Cl}$) and **99** [93JCS(P1)1403], **76** (92JOC-4859), **100** [$\text{R} = n\text{-C}_{15}\text{H}_{31}$ [93JCS(P1)1403], $\text{CH}=\text{CH}_2$, $\text{C}(\text{Me})=\text{CH}_2$ [91CC1638; 93JCS(P1)1403], and ferrocenyl (93CC417)], **101** (92JOC4859), **102** [$\text{A} = 1,1'$ -ferrocenediyl (93CC417) and CH_2 (92JOC4859)], and **103** (92JOC4859) have been prepared in moderate to excellent yields (Scheme 42).

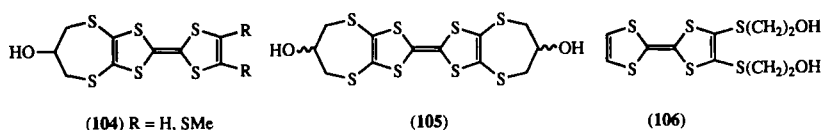
Some reactions of alcohols **104** with isocyanates (93T6849) have been reported, as have reactions of acyl halides with **104** ($\text{R} = \text{SMe}$), **105** (93T6849), and **106** (93CC417). In turn, alcohols of type **104** and **105** have been prepared by lithium aluminium hydride reduction of the corresponding ketones or through deprotection of their *O*-*tert*-butyldiphenylsilyl derivatives (91TL6033; 93T6849).



SCHEME 39



SCHEME 40

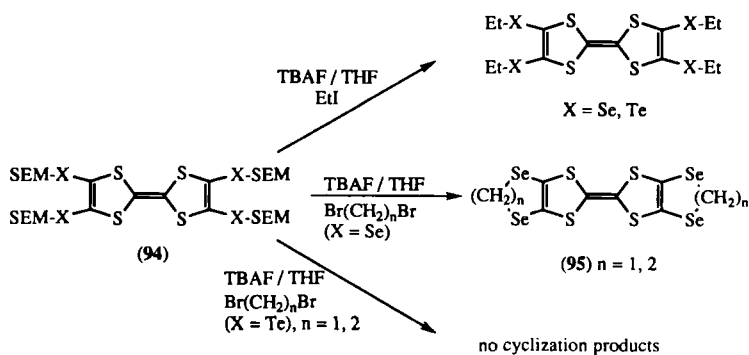


Alkoxy carbonylalkylthio substituents on tetrathiafulvalenes undergo hydrolysis to give the free acids (90T433; 92MI9; 92MI10) and have also been decarbomethoxylated to the corresponding methylthio derivatives (89CS71). A number of amides have been prepared from ω -carboxyalkylthiotetrathiafulvalenes (91MI2).

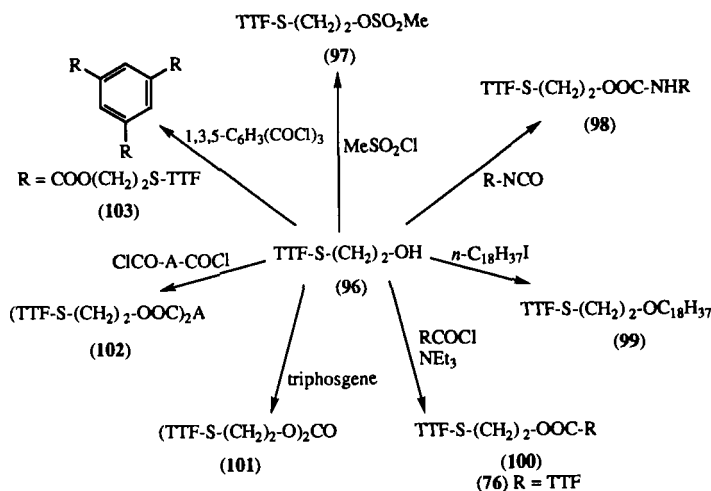
A variety of substitution and elimination reactions on **97** have been carried out [91CC1638; 93JCS(P1)1403]. Using a similar methodology, the first tetrathiafulvalenes containing amino groups (**108**) were synthesized from **107** (90T433) (Scheme 43).

Multiple eliminations on **109** and **110** ($\text{X} = \text{Cl}$) have been reported (91CC1638), as well as a fourfold substitution on **110** ($\text{X} = p\text{-ClC}_6\text{H}_4\text{SO}_3$) (91UKZ107) (Scheme 44).

The intramolecular coupling of **111** affords **112** (91CC843). The exact stereochemistry of **112** remains unknown (the *cis/cis* isomer is depicted)



SCHEME 41

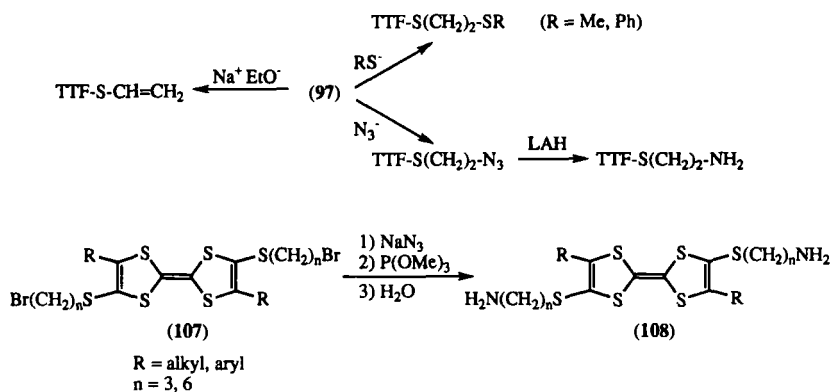


SCHEME 42

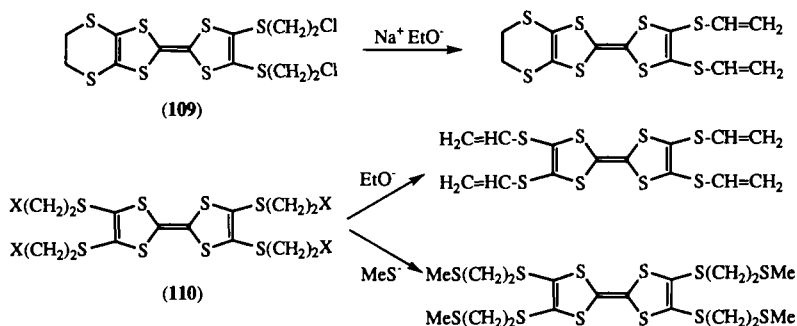
because the acidic conditions used to generate the dithiolium cations can induce *cis/trans* isomerization (Section II.B.2) (Scheme 45).

5. Halo Groups

Only a few halotetrathiafulvalenes are known (Section II.C.6.c), so it is not surprising that their chemistry has not been widely studied. However, two reactions carried out on **113** are worth mentioning [86H(24)1145]. The first reaction is the metal-halogen exchange, which affords **1** in nearly



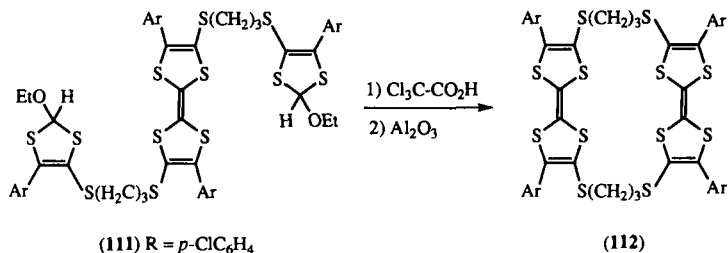
SCHEME 43

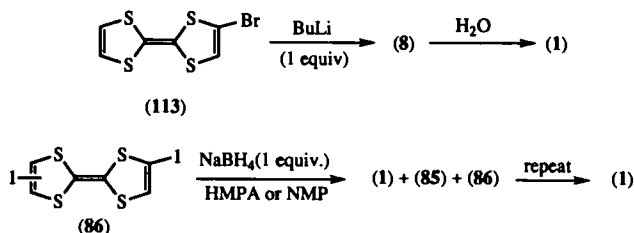


quantitative yield (Scheme 46), and the second is the base-catalyzed halogen dance reaction carried out with LDA, which yields a mixture of **1**, **113**, tribromotetrathiafulvalene and all possible isomers of dibromotetrathiafulvalene. Very recently, it has been reported that **86** can be deiodinated in a stepwise manner by reduction with sodium borohydride (94CC983) (Scheme 46). The four bromine atoms of tetrabromotetrathiafulvalene can also be removed consecutively through the addition of 1–4 equivalents of NaBH_4 . However, this reaction fails in the case of chlorotetrathiafulvalene derivatives.

6. Metallo Groups

Reactions discussed in this section are classified according to the nature of the TTF—element bond(s) formed in the reaction of TTF-Li (**8**) with electrophilic reagents. Only rarely have other metals, such as Mg, been used to this end, and reference is made to them where appropriate.

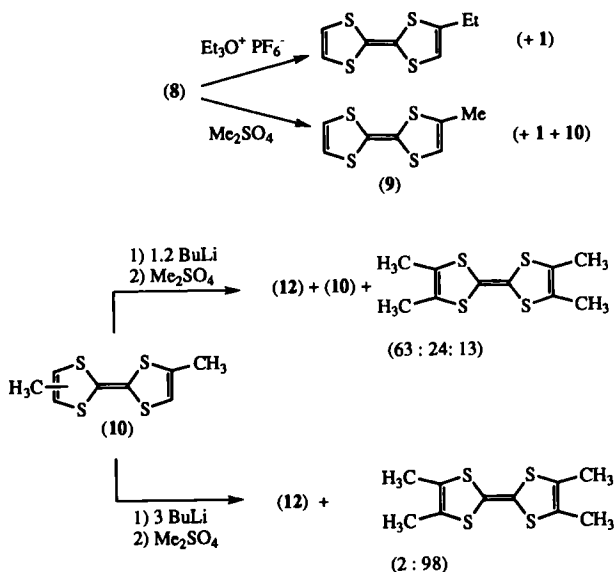




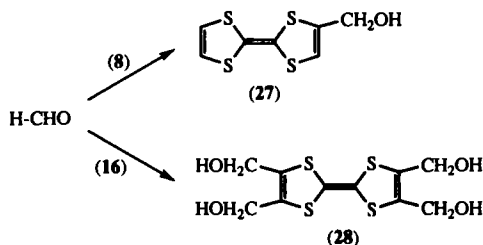
SCHEME 46

a. *Formation of TTF—C Bonds*

i. *Alkyl and Substituted Alkyl Groups.* The introduction of alkyl groups onto the TTF nucleus is not of practical importance owing to the drawbacks in purification associated with the coexistence of mono- and multisubstituted derivatives, as well as unreacted TTF. Another problem encountered in the synthesis of alkyltetrathiafulvalene compounds is that long-chain alkyl halides do not react with TTF—Li (90CC816). However, some reactions have been carried out on **1** (77CC161; 79JOC1476) and **10** (92BSB137) (Scheme 47).



SCHEME 47



SCHEME 48

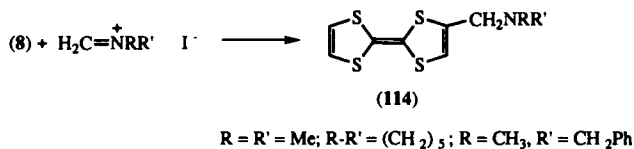
For coverage of the formation of TTF—aryl or —heteroaryl bonds using Mg or Sn derivatives, see Section II.C.6.g.

The reactions of formaldehyde with lithiated tetrathiafulvalenes **8** (79JOC1476) and **16** (88MI3) lead to the corresponding alcohols (Scheme 48). It is worth noting that a much improved synthesis of **27** has recently been described (94S489).

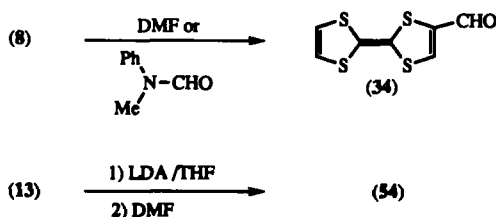
The synthesis of *N,N*-dialkylaminomethyltetrathiafulvalenes **114** has been described (91TL6407; 92T3983) (Scheme 49). The mass spectrometric behavior of these donors has been described (93RCM587), as well as some magnetic (93MI15) and structural properties [93AX(C)1184] of charge-transfer complexes derived from them.

ii. Formyl and Acyl Groups. Although several syntheses of formyltetrathiafulvalene (**34**) have been described in which DMF is used as a formylating agent (78CC832; 79JOC1476; 92MI6; 92MI7), it has been reported that *N*-methylformanilide is the reagent of choice for carrying out this reaction (94S489), even on a multigram scale. The same conclusion has been mentioned briefly in a recent paper (93JA3752) by Batail and co-workers. Aldehyde **54** has been synthesized from **13** using DMF as the formylating agent (93MI5) (Scheme 50).

The introduction of acyl groups other than formyl onto the TTF nucleus has usually been carried out through the reaction of TTF—Li (**8**) with acyl chlorides (79JOC1476; 88MI8; 90CC816; 93CC417; 94CM1419), although the use of Grignard derivatives has also been reported (89ZOR1456)



SCHEME 49



SCHEME 50

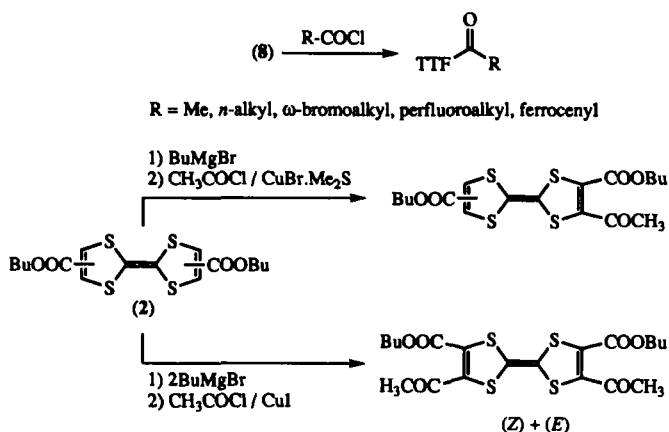
(Scheme 51). Some of the ketones in question have proved to be important in Langmuir–Blodgett film formation (88MI8; 91CSR355).

For a discussion of the introduction of acyl groups into the TTF core via silyl derivatives, see Section II.C.6.f.

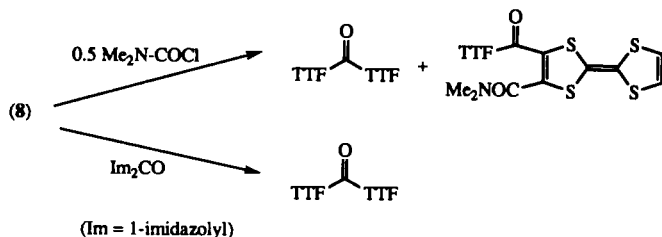
Acyating reagents other than acyl chlorides have rarely been used in this area (93MI16) (Scheme 52).

iii. Carboxy and Related Groups. The synthesis of tetrathiafulvalene-carboxylic acid **65** by the reaction of TTF—Li with carbon dioxide has been reported by several different groups (77CC161; 79JOC1476; 89MI5; 90CC816; 92BSB741; 94L549) with yields in the range 36–60%. Nevertheless, the best synthesis of **65** (94S489) involves isolation of the lithium carboxylate formed initially, followed by acidification with dilute hydrochloric acid. The synthesis of **71** has also been reported using a standard procedure (92BSB741) (Scheme 53).

The lithiation of TTF (**1**) (79JOC1476) and its methyl-substituted deriva-



SCHEME 51



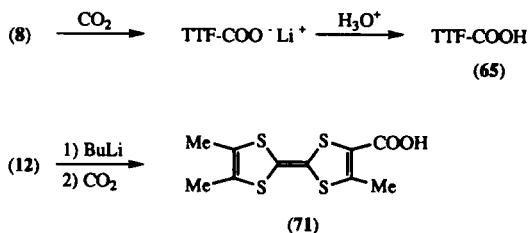
SCHEME 52

tives **9**, **10**, and **12** (79JOC1476; 92BSB741), followed by trapping with ethyl or methyl chloroformate, has given rise to the corresponding ethyl or methyl esters in moderate yields. Compounds **1** and **9** have also been dilithiated and have afforded the corresponding diesters (79JOC1476). Other tetrathiafulvalenes with one (79JOC1476) or two (89ZOR1456) ester groups undergo analogous reactions.

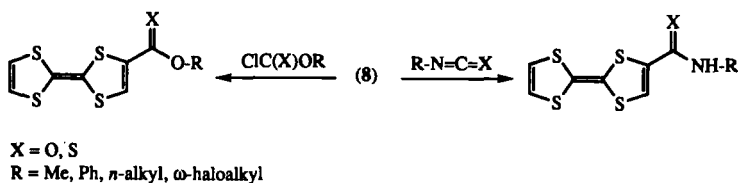
TTF—Li (**8**) has also been trapped with long-chain alkyl chloroformates and chlorothioformates [90CC816; 93PS(74)279; 94CM1419] (Scheme 54). This approach has allowed the synthesis of *O*-hexadecylthiocarboxy-tetrathiafulvalene, which forms stable, high-quality Langmuir–Blodgett films, which are highly conducting when doped with iodine (90CC970; 92CM724).

Finally, **8** reacts with isocyanates (94CM1419) and isothiocyanates (93CC1701; 93MI17; 94CM1419) to give the corresponding amides and thioamides (Scheme 54). 4-(*N*-Methylthioamido)tetrathiafulvalene is the first example of a neutral tetrathiafulvalene derivative to form a κ -phase structure (93CC1701).

b. Formation of TTF—Chalcogen Bonds. Reactions under this heading are classified into three different sections according to the number of



SCHEME 53



SCHEME 54

TTF—chalcogen bonds formed, rather than the nature of the newly formed (TTF—S, —Se, or —Te) bond(s).

i. **One TTF—Chalcogen Bond.** Elemental sulfur and selenium are the most widely used reagents for the introduction of these chalcogens onto the TTF nucleus via lithiation, although other sources of electrophilic S or Se have been employed (see below). In contrast, elemental tellurium is the only Te-based reagent used so far in this type of reaction.

The lithium tetrathiafulvalenechalcogenolate thus formed (**115**) is then trapped with the appropriate alkylating or acylating reagent [90CC816; 91CC1638; 91MI5; 92JOC4859; 93JCS(P1)1403; 93MI17] (Scheme 55).

Other reagents for the formation of TTF—S bonds include thiuram disulfides (93UP1) and di(phenylsulfonyl) sulfide (92TL1783) (Scheme 56). The use of SEM disulfide is referred to below.

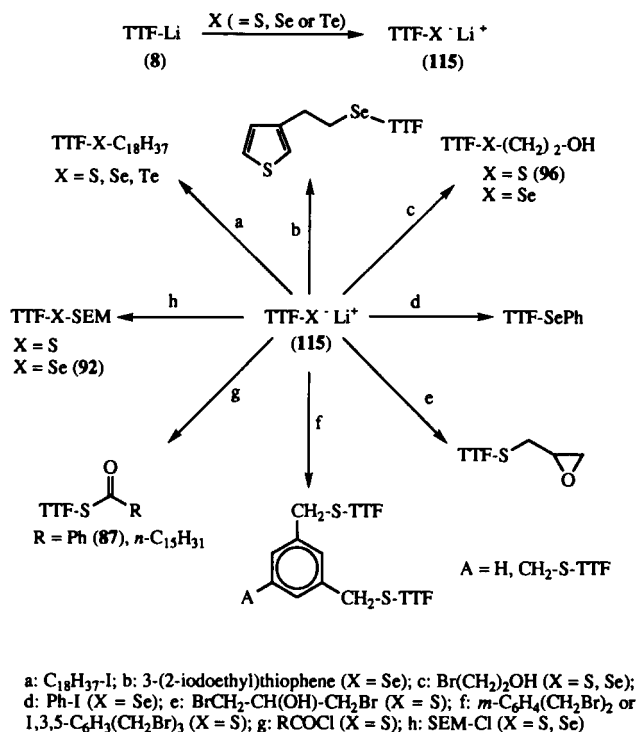
Linking of Se atoms to the TTF nucleus has occasionally been carried out with different reagents, such as PhSeCl (82OM1311), PhSeSePh [93JCS(P1)1403], and di(phenylsulfonyl) diselenide (92TL1783) (Scheme 57).

The formation of TTF—Te bonds is carried out by reacting lithiated tetrathiafulvalenes with elemental tellurium. Two very surprising reactions that tetralithiated TTF undergoes have been described (88TL6177; 92CC1048) (Scheme 58). A detailed structural and electronic study of these two donors has recently been reported (93CM1199).

ii. **Two TTF—Chalcogen Bonds.** When only two vinylic hydrogen atoms are available for proton–lithium exchange, e.g., on a disubstituted tetrathiafulvalene, the lithiation–chalcogenation sequence can be carried out to afford a derivative bearing two new TTF—chalcogen bonds. A number of examples of this transformation starting from **13** have been described [91ZN(B)1269; 92PS(67)333] (Scheme 59).

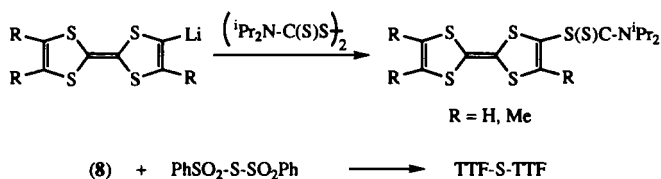
When TTF itself (**1**) is treated with two equivalents of LDA, the resulting 4,4'(5')-dilithio derivative **14** reacts in a similar fashion (85TL2783) (Scheme 60).

Some striking results concerning the formation of 4,5-bis(alkylthio)tetrathiafulvalene derivatives from TTF—Li have recently been reported

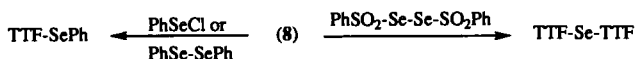


SCHEME 55

[93JCS(P1)1403; 93PS(74)279]. Under carefully controlled conditions, the reaction of **8** with 1.5 equivalents of elemental sulfur (or selenium), followed by treatment with 1 equivalent of 1,2-dibromoethane affords EDT—TTF (**13**) (or its ethylenediseleno analog) in a one-pot sequence, albeit in low yields. It has been reported that varying the molar ratio of reactants does not lead to an increase in the yield (Scheme 61).



SCHEME 56

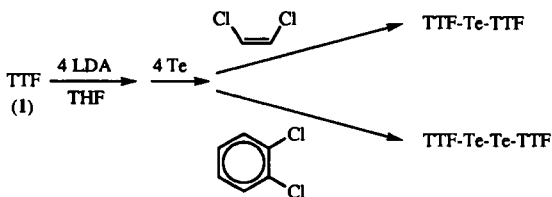


SCHEME 57

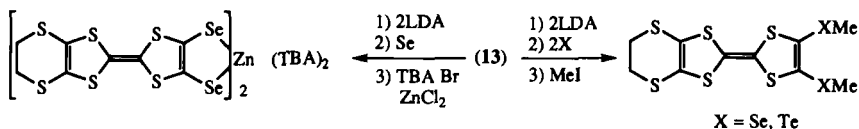
iii. **Four TTF—Chalcogen Bonds.** Sequential treatment of tetralithio-tetrathiafulvalene **16** with elemental selenium or tellurium and alkyl halides is a widely used method for the synthesis of tetrakis(alkylchalcogeno)tetrathiafulvalenes (86CL1861; 87CL2265; 87JOC3444; 88MI5). The synthesis of tetrakis(ethyltelluro)tetrathiafulvalene through this approach represents the first example of tetralithiation of TTF (85TL2783) (Scheme 62).

Tetrakis(methyltelluro)tetrathiafulvalene is a single-component organic semiconductor [87N(L)(329)39], and other related long-chain derivatives have been studied [92PS(67)367], mainly in connection with the so-called "fastener effect" (87PAC999).

Early attempts to react tetrathiafulvalenetetrachalcogenolate anions with alkylene dihalides, such as dichloromethane or 1,2-dibromoethane, did not meet with success. Unidentified dark solids were obtained (85TL2783) on treating the tetratellurolate anion with such dihalides, and similar results were reported (87MI7) when both tetraanions were made to react with $\text{Br}(\text{CH}_2)_n\text{Br}$ ($n = 1$ or 2). Only polymeric products were obtained, even under high dilution conditions. Sometime later, however, bis(ethylenediseleno)tetrathiafulvalene was obtained by this route, although in low yields (88MI3). Given the importance of this kind of donor, two different improvements were devised with a view to favoring the intra-over the intermolecular alkylation reaction. The first one used SEM—Cl as a protecting group on the tetraselenolate anion (87MI7) (Section II.C.4.a). The second improved method (88MI4; 89CC169) avoided the use of the expensive SEM—Cl and its main features were (i) the replacement of THF with HMPA as solvent, which was thought to favor intramolecular alkylation, and (ii) the addition of sodium borohydride in order to cleave



SCHEME 58



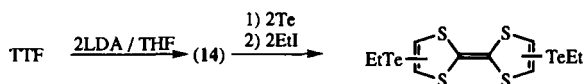
SCHEME 59

any intermediate with Se—Se linkages. In this way, various bis(alkylenedi-seleno)tetrathiafulvalenes were prepared in good yields (medium after recrystallization) (Scheme 63).

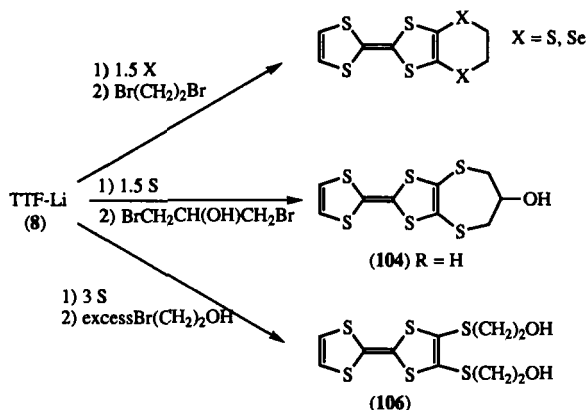
The Se—SEM groups can also be introduced onto the TTF nucleus in a different way, which involves (91TL2741) the reaction of tetralithiated tetrathiafulvalene **16** with SEM—Se—Se—SEM. The analogous sulfur compound, SEM—S—S—SEM, works in a similar way, thus allowing the formation of four TTF—S bonds. Indeed, treatment of TTF **1** with four equivalents of LDA, followed by four equivalents of the corresponding SEM dichalcogenide, gives a mixture of mono-, di-, tri-, and tetrasubstituted tetrathiafulvalenes in a 66–75% overall yield. These compounds can easily be separated by column chromatography, and the SEM groups can then be removed in the usual way (Scheme 64). It is noteworthy that although four equivalents of base is used, a mixture of all possible substituted products is obtained, and this has been interpreted as a consequence of the disproportionation equilibrium proposed by Green (79JOC1476). In spite of the mixture of products obtained, the versatility of the method lies in the easy separation of the (X—SEM)-substituted products, which eventually gives rise to pure tetrathiafulvalenes with different numbers of chains.

A similar situation (i.e., formation of all possible substituted products starting from **1** and four equivalents of LDA) has been reported [91CR(II)(313)1395] when phenylselenenyl chloride is used as the electrophilic reagent (Scheme 65).

On the other hand, good yields of tetraselenated products have been obtained (87JOC3444) by treatment of **16** with four equivalents of dialkyl (aryl) diselenides. Analogous reactions with dialkyl(aryl) disulfides are also satisfactory, but it was reported in the same paper that the reaction



SCHEME 60

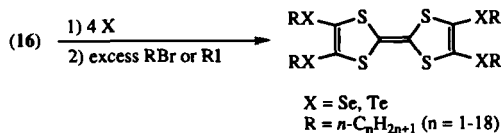


SCHEME 61

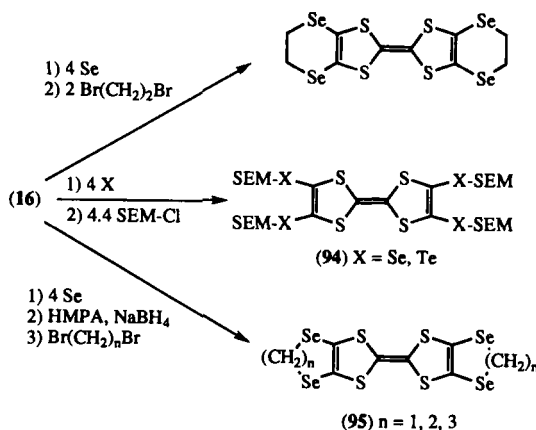
of **16** with four equivalents of elemental sulfur did not lead to the expected tetrakis(alkylthio)tetrathiafulvalenes (Scheme 66).

Nevertheless, the synthesis of the tetrathiafulvalenetetrathiolate anion has indeed been carried out very recently, starting from TTF and elemental sulfur (93JOC6480; 93MI6). Important as the tetrathiafulvalenetetrathiolate reagent may be, it is perhaps not surprising that its synthesis by this approach had not been carried out previously, given the literature precedents (87JOC3444) and its relatively easy access by other routes starting from dithiapendione (77JA5521), **88** [85ZOR1582; 91JCS(P2)1963], and **89** (92TL3923). For example, treatment of **1** with 10 equivalents of LDA in THF followed by 4.1 equivalents of sulfur leads to the tetrathiolate anion, which can be isolated by precipitation with hexane. The yield is nearly quantitative and the product has been made to react with either excess methyl iodide or various Pt or Ni compounds to afford new coordination complexes of tetrathiafulvalenetetrathiolate (Scheme 67).

It was shown in the same study that the use of only 4 equivalents of LDA and 4.1 equivalents of sulfur, followed by reaction with excess methyl iodide (without isolation of the presumed tetraanion), leads to a



SCHEME 62

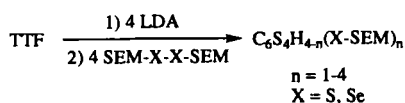


SCHEME 63

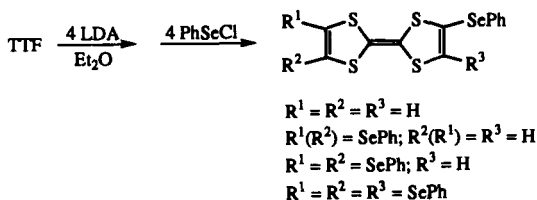
mixture of all possible substituted derivatives, with different product ratios being obtained from run to run. This seems to be due to the highly sensitive nature of the numerous equilibrium reactions taking place. Moreover, under these conditions, the yield of tetrakis(methylthio)tetrathiafulvalene is $\sim 35\%$ and can only be increased to $\sim 50\%$ if the mixture of lithium thiolates is first isolated by precipitation and then quenched with MeI. In this way it has been demonstrated, contrary to previous reports (91TL2741), that an excess of base (LDA) can shift the equilibrium between TTF **1** and its tetraanion **16**.

c. *Formation of TTF—Halogen Bonds.* Chloro-, bromo-, and iodotetrathiafulvalenes have been prepared using the metallation methodology. Given the electron-withdrawing properties of these substituents and the disproportionation reactions of TTF—Li, it is not surprising that dihalotetrathiafulvalenes are common side products when the corresponding monohalo derivatives are sought.

A variety of halogenating agents have been reacted with TTF—Li in order to obtain the corresponding mono- and/or dihalotetrathiafulvalenes:



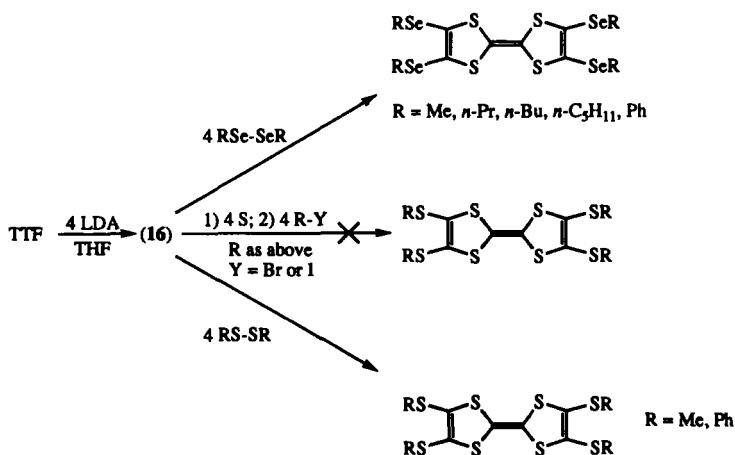
SCHEME 64



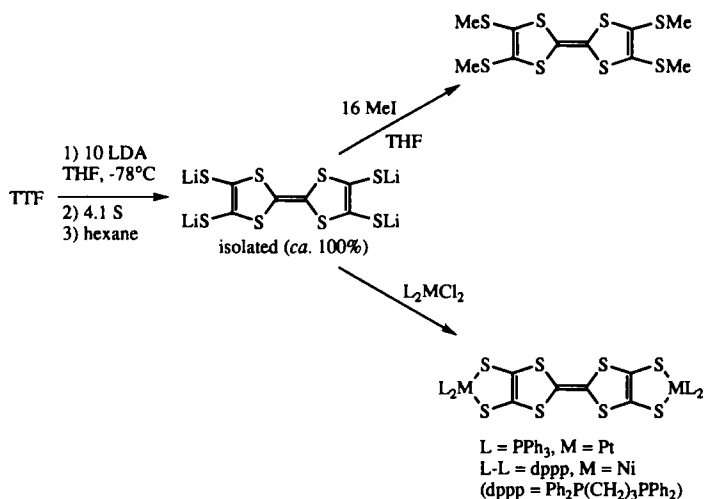
SCHEME 65

tosyl halides (91S263), 1,2-dibromotetrachloroethane (91CC92), bromine, *N*-chlorosuccinimide [86H(24)1145], and perfluorohexyl iodide (94CC983) (Scheme 68).

It is interesting to note that the 4,5-disubstituted tetrathiafulvalene is the usual by-product. This is possibly due to the electron-attracting nature of the halogen substituent, which accelerates the disproportionation process of the lithiated species and directs the second lithiation to the adjacent position. However, the isolation of the 4,4'(5')-dichloro and -dibromo isomers has been reported in one instance [86H(24)1145]. The formation of **86** may result from the steric hindrance created by the two neighboring iodine atoms, which would also account for the lack of formation of any tetraiodo derivative under the reaction conditions (94CC983). When 1,2-dibromotetrachloroethane was used as a halogenating reagent, higher substituted tetrathiafulvalenes were also obtained and the relative ratio of all possible isomers was found to be dependent on the base used. With LDA,



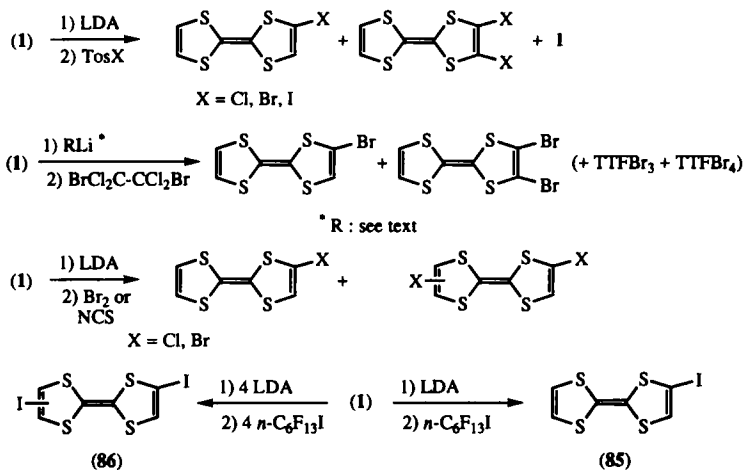
SCHEME 66



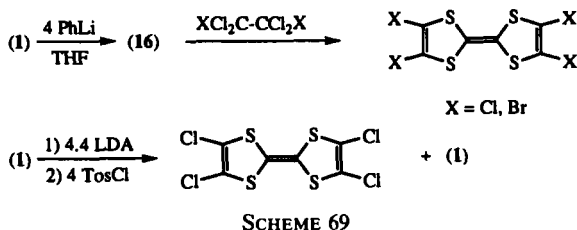
SCHEME 67

PhLi, or LiHMDS, the corresponding TTFBr_2 : TTFBr ratios were 3.8 : 1, 2.1 : 1, and 1.6 : 1 respectively, together with smaller amounts of TTFBr_3 and TTFBr_4 . On the other hand, the use of MeLi led to a 1 : 2.7 molar ratio of TTFBr_2 : TTFBr with no higher bromo analogs being detected.

Tetrahalotetrathiafulvalenes (89S207; 91S263) have been prepared in



SCHEME 68

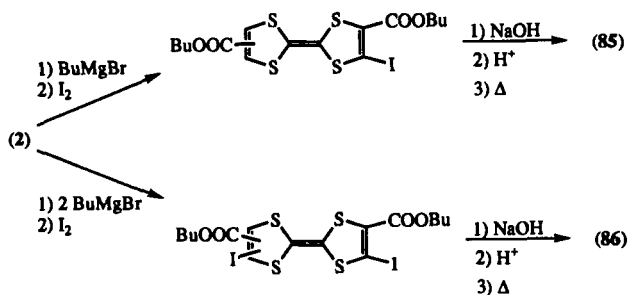


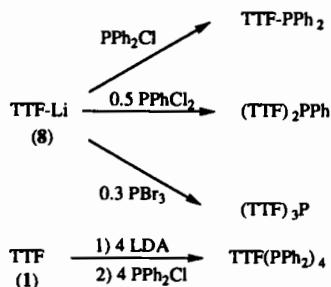
low to moderate yields from **16** (Scheme 69), although tetraiodotetrathiafulvalene could not be obtained either by the reaction of **16** with iodine (89S207) or with tosyl iodide (91S263).

Compounds **85** and **86** have also been prepared from **2** via reaction of its mono- and di-Grignard derivatives with iodine, followed by hydrolysis and decarboxylation (89ZOR1456) (Scheme 70).

d. *Formation of TTF—P Bonds.* New derivatives with one or more TTF—P bonds have been developed by Batail and co-workers [91CC1370; 92BSF29; 93AX(C)1936; 93OM797; 93PS(75)175]. These derivatives are particularly interesting, not only as precursors for new mixed-valence salts or as new multistage redox systems, but also because of their ability to coordinate to metallic species. Tetrathiafulvalene and some methyl-substituted tetrathiafulvalenes have been lithiated and made to react with halophosphines, affording, in some cases, new nonplanar donors where a P atom links two or three TTF moieties (Schemes 71 and 72).

The results of the electrooxidation of diphenyl(trimethyltetrathiafulvalenyl)phosphine in the presence of $(\text{TBA})_2 \text{Mo}_6\text{Br}_{14}$ have recently been reported [93AX(C)1936].

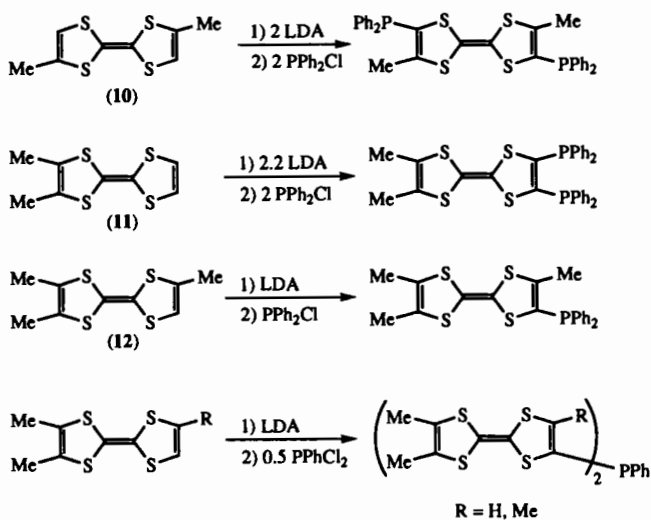




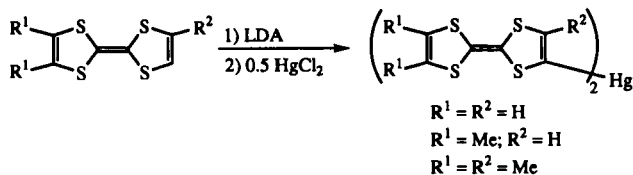
SCHEME 71

Thus far, TTF derivatives linked to an sp^3 -nitrogen atom have not been reported. All attempts to synthesize any of these derivatives from TTF—Li via electrophilic amination have proved unsuccessful (92MI5).

e. Formation of TTF—Hg Bonds. A number of compounds in which a mercury atom links two tetrathiafulvalene moieties have been prepared in order to determine the extent of interaction between the two redox units in these dimers (93OM797) (Scheme 73). The reactions have been carried out starting from TTF (1), 4,5-dimethyltetrathiafulvalene (11), and trimethyltetrathiafulvalene (12), although preliminary experiments indi-



SCHEME 72

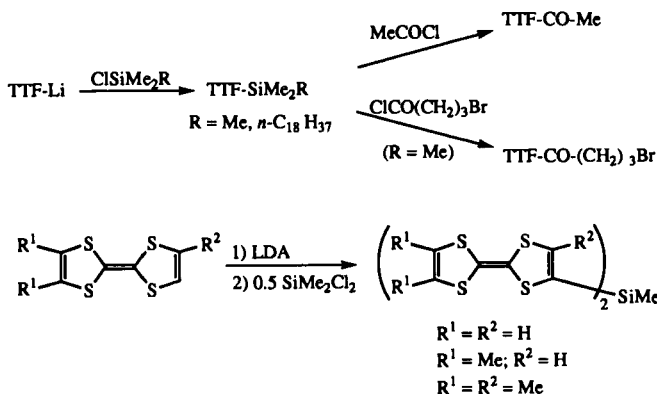


SCHEME 73

cate (93S509) that 4'-methyl-4,5-ethylenedithiotetrathiafulvalene behaves in a similar way. Several charge-transfer complexes of these donors have been prepared (93OM797).

f. *Formation of TTF—Si Bonds.* Very few examples of the reaction of lithiated tetrathiafulvalenes with chlorosilanes are known (90CC816; 93OM797) (Scheme 74). Nevertheless, some monosubstituted trialkylsilyl derivatives have been described (90CC816), and they are synthetically useful to some extent since TTF—SiMe₃ can behave (in certain cases) as a shelf-stable equivalent of TTF—Li, although tin compounds, such as TTF—SnR₃ (Section II.C.6.g), seem to be more efficient reagents. Some compounds containing two TTF—Si bonds have also been prepared, and it has been reported that electrocrystallization of some of these donors results in the breaking of the TTF—Si bond [93OM797; cf. 91AG(E)1498].

g. *Formation of TTF—Sn Bonds.* Tributyl- and trimethyl-stannyltetrathiafulvalenes (**116** and **117**) have been prepared in good yield (92CC158) from TTF—Li, and their synthetic versatility has been demonstrated by their palladium-catalyzed cross-coupling reactions with aryl halides (Stille



SCHEME 74

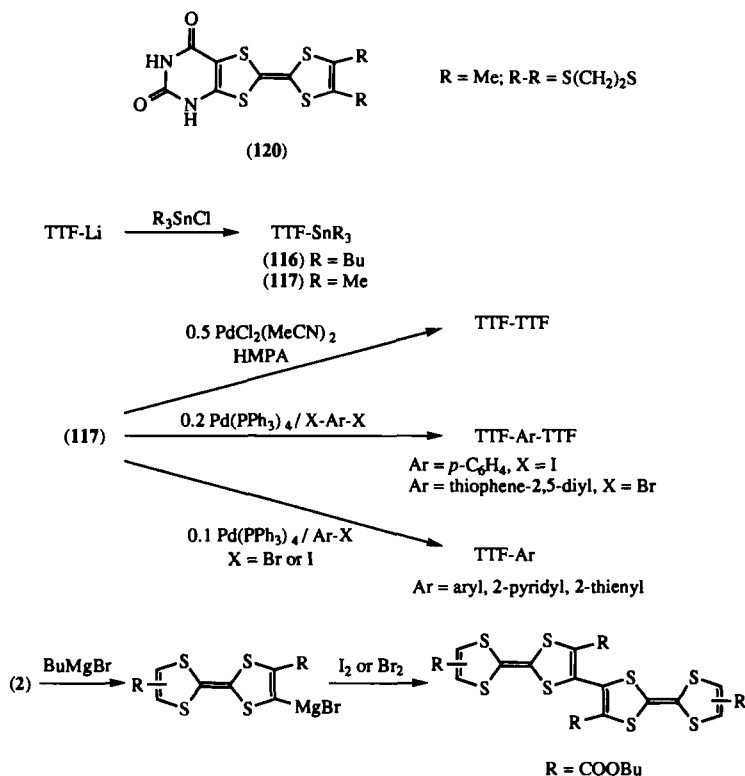
reaction). The homocoupling of **117** is somewhat reminiscent of the oxidative coupling of the Grignard derivative of **2**, which can be carried out with bromine or iodine (89ZOR1456) (Scheme 75).

7. Fused Heterocyclic Rings

The study of the chemistry of heterofused tetrathiafulvalenes is in its infancy and only a few examples are available. Isothiazolo derivative **118** affords, upon hydrolysis of the nitrile group and decarboxylation, the rearranged product **119** (87MI8) (Scheme 76). Similar reactions with unsymmetric tetrathiafulvalenes have also been reported (90MI4).

Dieckmann condensations giving rise to thieno-fused tetrathiafulvalenes have recently been reported (93KGS761) (Scheme 77).

Symmetric and unsymmetric pyrimidotetrathiafulvalenes, such as **120**, have been *N*-alkylated or *N,N'*-dialkylated via their tetrabutylammonium salts (92KGS1122).



SCHEME 75



SCHEME 76

III. Reactivity of Tetraselenafulvalenes

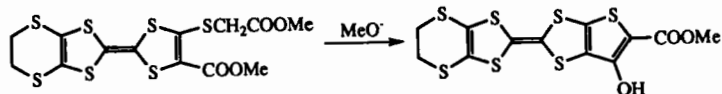
A. GENERAL SURVEY

The chemistry of tetraselenafulvalenes resembles that of their sulfur-containing counterparts in many respects, but it is less well developed—a fact that is partly due to the synthetic difficulties associated with the preparation of the tetraselenafulvalene core (use of toxic or not easily available starting materials, etc.).

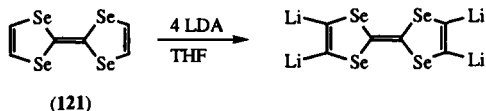
Tetraselenafulvalene (TSF) can be lithiated, although the scope of this reaction is more restricted than in the case of TTF (Section III.B). Only a few substituents have been introduced into the TSF core to date, and their reactions, which are quite similar to those of the analogous tetrathiafulvalenes, are discussed in Section III.C.

B. REACTIVITY AT THE RING ATOMS

The reaction of TSF (**121**) with organolithium derivatives is the only process to be treated in this section, and its outcome largely depends on the reagent used. The first report concerning the lithiation of **121** appeared at the same time as that for the lithiation of TTF. Green reported (77CC161) that treatment of TSF with BuLi, followed by reaction with carbon dioxide, afforded tetraselenafulvalenecarboxylic acid, in a way similar to the synthesis of tetrathiafulvalenecarboxylic acid. Nevertheless, no experimental details were given and this early claim has not yet been confirmed. Indeed, Cava and co-workers found (88CC1089) that treatment of TSF with one equivalent of butyllithium led to complete destruction of the



SCHEME 77



SCHEME 78

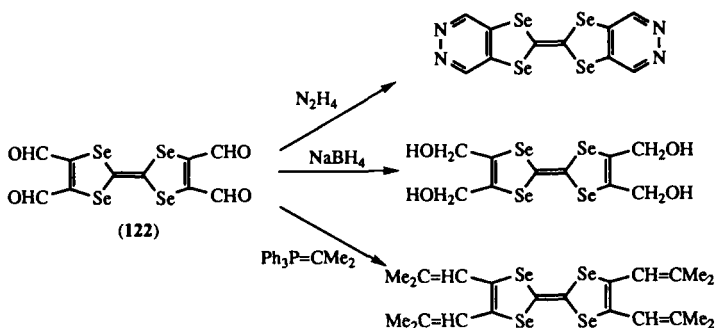
heterocycle, with the formation of several products, such as $\text{BuCH}=\text{CH}-\text{SeBu}$ and $\text{BuSeCH}=\text{CHSeBu}$. Thus, it seems that an anionic attack at carbon or selenium is favored instead of the desired lithium-hydrogen exchange.

Tetralithiotetraselenafulvalene was, however, generated (88CC1089) from TSF by using four equivalents of LDA in THF and since then, this has been the reagent of choice for carrying out this reaction (Scheme 78). As a consequence, tetrasubstituted tetraselenafulvalenes are usually obtained, although some monosubstituted derivatives have been reported (91TL2741; 93S465) (Section III,C,3). It is worth noting that disproportionation equilibria must also play a role in the case of TSF, since it has been reported (91TL2741) that treatment of TSF with LDA (four equivalents) leads to a mixture of mono-, di-, tri-, and tetrasubstituted derivatives.

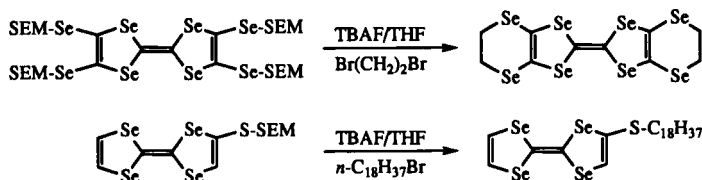
C. REACTIVITY OF SUBSTITUENTS

1. C-Linked Substituents

As in the case of tetrathiafulvalenes, formyl groups are synthetically useful. Some mono- and 4,5-diformyltetraselenafulvalenes have been re-



SCHEME 79



SCHEME 80

duced to the corresponding alcohols (93MI18; 93MI19) and the reactivity of **122** has been investigated (89CC1520) (Scheme 79).

The decarbomethoxylation of $\text{TSF}(\text{COOMe})_4$ to afford **121** is of importance, since it constitutes the first example of this versatile reaction in tetrachalcogenafulvalene chemistry (76JOC882) (cf. Section II.C.2.d).

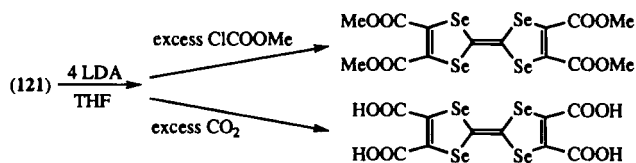
2. *S*- and *Se*-Linked Substituents

Compounds of general formula $\text{TSF}(\text{X-SEM})_n$ ($n = 1-4$; $\text{X} = \text{S}, \text{Se}$) are easily transformed into *S*- or *Se*-alkylated derivatives of TSF under standard conditions (91TL2741) (Scheme 80).

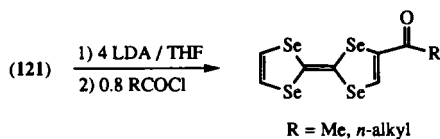
3. Metallo Groups

a. *Formation of TSF—C Bonds.* The direct introduction of four *C*-linked groups by the reaction of tetralithiated tetraselenafulvalene with electrophiles has been reported (88CC1089) (Scheme 81).

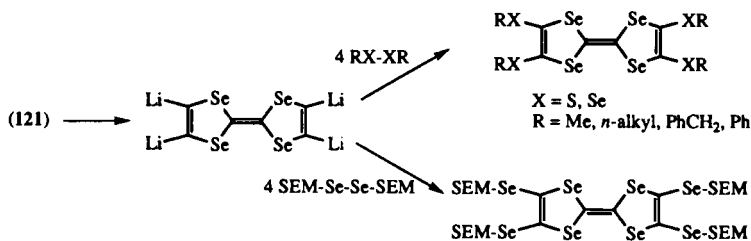
On the other hand, the introduction of only one *C*-linked substituent is difficult, the first report of such a monofunctionalization of TSF, without the formation of multisubstituted derivatives, is very recent (93S465) and shows that quite different conditions are needed to carry out this reaction than those used to monofunctionalize TTF. The synthetic strategy involves the generation of the tetraanion, followed by trapping with less than one equivalent of the corresponding electrophile (acyl halides were used). The main drawback with this method is that the desired products



SCHEME 81



SCHEME 82



SCHEME 83

are prepared in low yields, although unreacted TSF can be recovered in ~60% yield (Scheme 82).

b. *Formation of TSF—Chalcogen Bonds.* The introduction of alkylthio and alkylseleno groups into the TSF nucleus is one of the most widely used reactions. The process makes use of dialkyl or diaryl disulfides (or diselenides) [87CL2265; 87CL2399; 88CC1089; 88MI5; 92MI11; 92PS (67)367], since direct insertion of elemental sulfur or selenium into the C—Li bonds of tetralithiotetraselenafulvalene does not give the expected products (93S465) or, if formed, they are accompanied by numerous by-products (87CL2399; 88MI5). The reaction of SEM dichalcogenides with tetralithiotetraselenafulvalene affords a mixture of mono- and polysubstituted derivatives which can be easily separated and which are synthetically useful (91TL2741) (Scheme 83).

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Organometallics in Coupling Reactions in π -Deficient Azaheterocycles

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I. Introduction	306
II. Cross-Coupling by Hydrogen Substitution	307
A. Alkenylation by Palladium Catalysis	307
1. General	307
2. Alkenylation Reactions	307
B. Alkynylation by Palladium Catalysis	314
1. General	314
2. Alkynylation Reactions	314
III. Cross-Coupling by Metal Substitution	330
A. Organotin Compounds (Stannanes)	330
1. General	330
2. Halogeno- and Triflyloxy-azines	330
3. Stannylation and Reactions of Stannylazines	349
B. Organoboron Compounds	358
1. General	358
2. Halogenoazines	358
3. Boronation and Reactions of Azinoboranes	365
C. Organoaluminum Compounds	371
1. General	371
2. Halogeno- and Triflyloxy-azines	371
D. Organozinc Compounds	372
1. General	372
2. Halogeno- and Triflyloxy-azines	375
3. Zincation and Reactions of Azinozinc Compounds	381
E. Organomagnesium Compounds	384
1. General	384
2. Sulfenylazines	384
3. Halogenoazines	386
F. Organocopper Compounds	393
1. General	393
2. Halogeno- and Triflyloxy-azines	393
3. Cupration and Reaction of Azinocopper Compounds	397
G. Organomercury Compounds	399
1. General	399
2. Halogeno- and Triflyloxy-azines	399
3. Mercuration and Reactions of Azinomercurials	400

H. Organomagnesium Compounds in Reactions with Sulfinylazines	403
1. General	403
2. Organomagnesium Reactions with Sulfoxides	403
IV. Homo-Coupling	406
A. Nickel Catalysis in Reactions of Halogenoazines	406
1. General	406
2. Low-Valent Nickel-Catalyzed Homo-Coupling	406
B. Homo-Coupling Mediated by Other Metals	409
1. General	409
2. Halogenoazines	411
3. Metalloazines	411
References	412

I. Introduction

Heterocyclic chemistry is undergoing a dramatic change with the coming of organometallic reactions for the construction of heterocycles and for carbosubstitution. The opportunities offered for carbosubstitution in all types of heterocyclic systems is especially important for future work and further studies.

Just a short time ago, substitutions in π -deficient heterocycles were generally limited to reactions with heteronucleophiles for the replacement of heterosubstituents, which frequently arise as part of the cyclization process in the preparation of the heterocycle or as part of a naturally occurring heterocycle, e.g., a hydroxy group in a pteridine or in the base moiety of a nucleoside. The importance of this development is obvious when it is desirable to have a readily prepared series of carbosubstituted analogs in a heterocyclic system, e.g., in biological fields.

Since this is the first review of its type for heterocycles, we want the heterocyclic chemist to become quickly familiar with reagents and reaction conditions. We therefore have chosen to present the material detailed in schemes rather than summarizing results in tables where much of the instructive information is lost. This method of presentation allows the reader with limited experience in organometallics to browse through the schemes in search of reagents and conditions suitable for a solution to his or her chemical problem.

II. Cross-Coupling by Hydrogen Substitution

A. ALKENYLATION BY PALLADIUM CATALYSIS

1. General

A variety of arenes and heteroarenes react with alkenes in the presence of palladium(II) derivatives to produce alkenyl substitution products. Three methods are commonly employed for the in situ preparation of palladium derivatives: (i) direct metallation of an arene or heteroarene with a Pd(II) salt; (ii) exchange of the organic group from a main-group organometallic to a Pd(II) compound; (iii) oxidative addition of an organic halide, an acetate, or triflate salt to Pd(0) or a Pd(0) complex. For catalytic reactions Cu(II) chloride or *p*-benzoquinone is usually used to reoxidize Pd(0) to Pd(II).

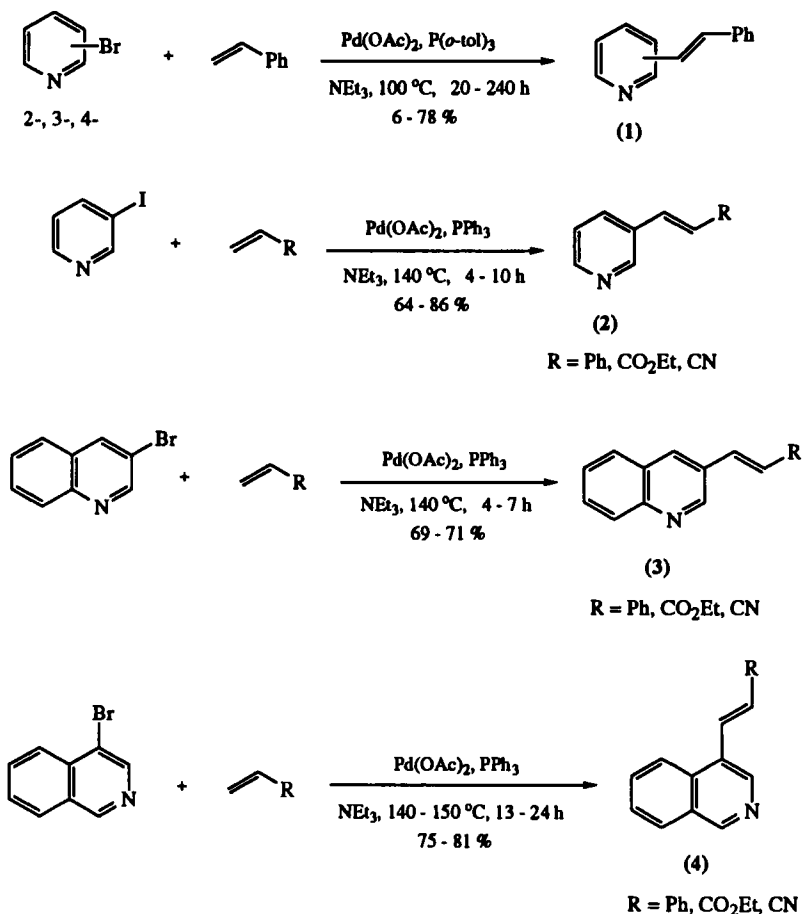
If two hydrogens on a β -carbon are available, elimination to (*E*)-alkenes is strongly preferred. If only one hydrogen is present on the β -carbon, the stereochemistry can be predicted on the basis of *syn*-addition of the organopalladium group to the double bond, followed by *syn*-elimination of a palladium hydride (91MI1).

2. Alkenylation Reactions

a. *Pyridine and Quinoline.* An early report (1978) on the alkenylation reaction in pyridines (78JOC2947) by Heck and co-workers, showed that Pd(OAc)₂, together with tri-*o*-tolylphosphine and triethylamine, would catalyze cross-coupling reactions between bromopyridines and styrene. The 2- and 4-pyridine isomers reacted slowly to form the vinylated pyridine (**1**) in low or moderate yields, whereas 3-bromopyridine was highly active in this reaction (Scheme 1). The same reaction between 3-iodopyridine and styrene with triphenylphosphine as ligand was reported to give vinyl substitution (**2**). Also successful were alkenylation reactions with ethyl acrylate or acrylonitrile to give the coupling products (**2**) with the (*E*)-configuration (79CPB193).

The fused pyridines, 3-bromoquinoline and 4-bromoisoquinoline, are both alkenylated by ethyl acrylate or styrene (**3**, **4**). The reaction with acrylonitrile was less satisfactory, especially in the 4-position in isoquinoline (78JOC2947; 79CPB193).

The alkenylated product (**5**) results from reactions of 2-iodo-4-methylquinoline with Pd(OAc)₂ as catalyst (Scheme 2). Minor amounts of homo-coupled 4,4'-dimethyl-2,2'-biquinoline accompany the reaction. Triphe-

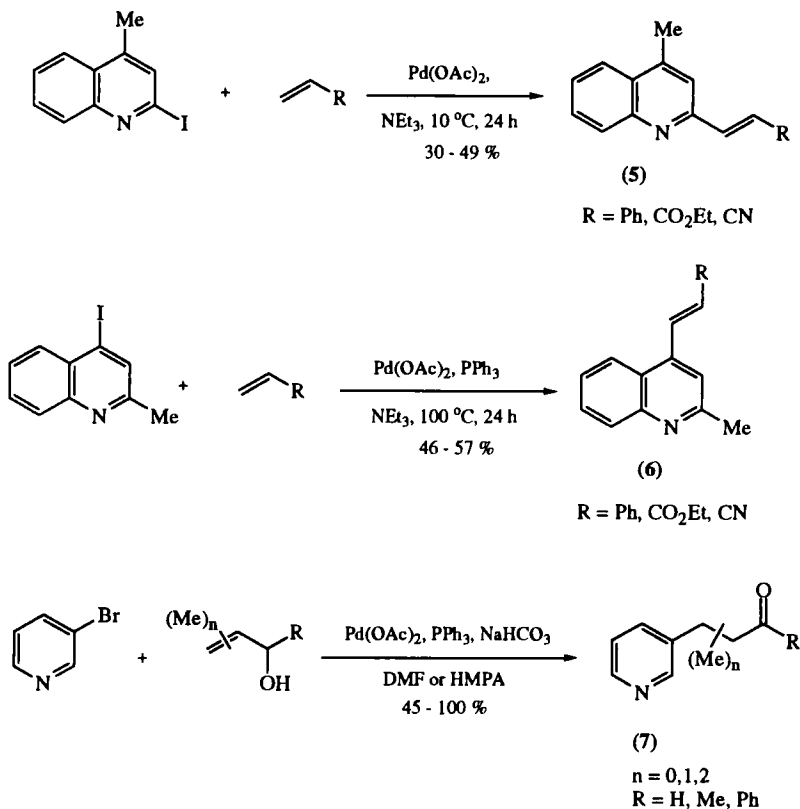


SCHEME 1

nylphosphine as ligand is deleterious for the preparation of **5**, but the phosphine ligand is necessary to effect cross-coupling of the 4-iodo isomer with formation of **(6)** (82CPB3647).

Allylic alcohols react differently. The coupling product has a saturated carbon chain in which the hydroxyl group has been oxidized to a formyl or keto group (**7**). The yields from 3-bromopyridine were generally high; a methyl group on an olefinic carbon in the alcohol retards the reaction (78JOC3396).

b. *Pyrimidine*. The alkenylation protocol between styrene, ethyl acrylate, or acetonitrile and a 5-bromo- or 5-iodopyrimidine gives the coupling

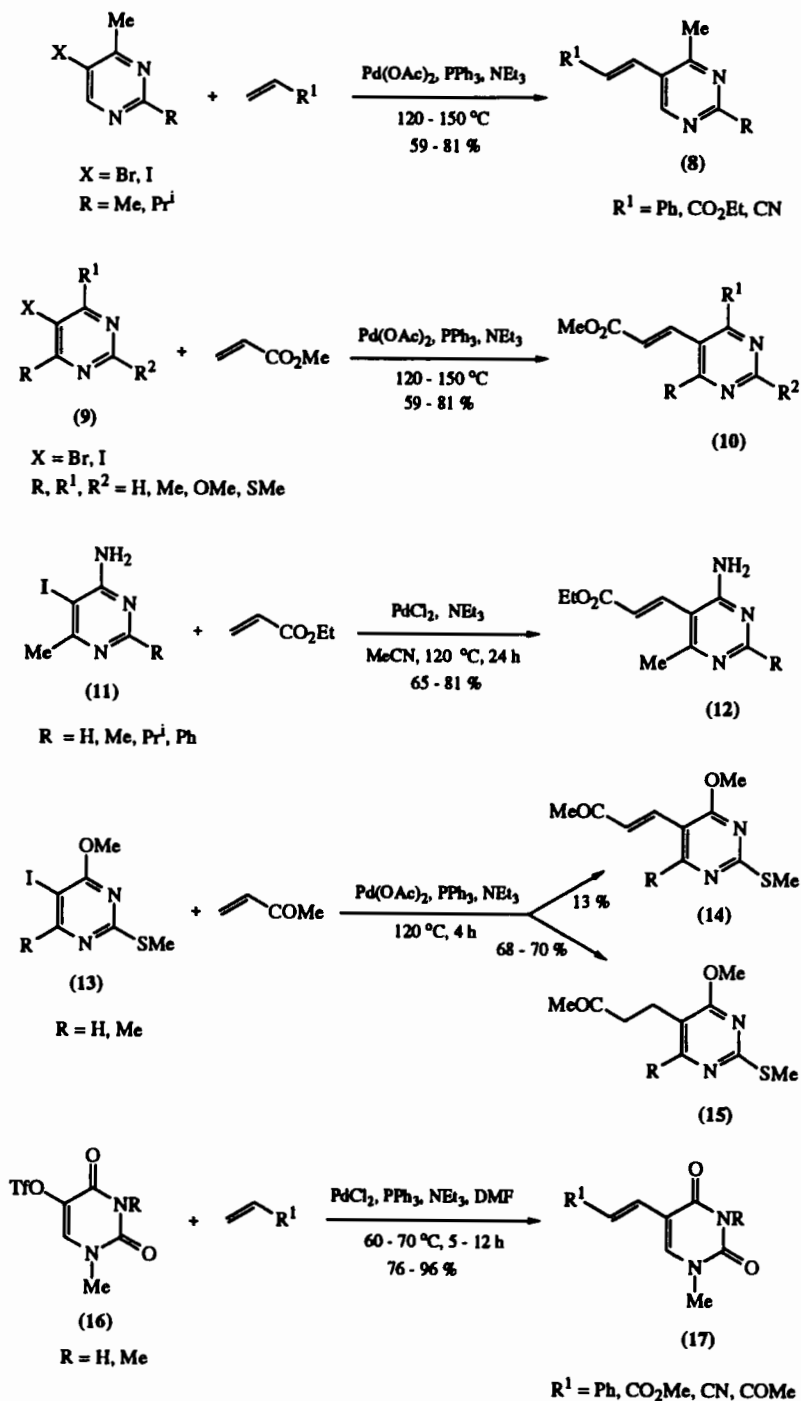


SCHEME 2

product (8) (Scheme 3). The 5-position in a pyrimidine is benzenoid (79CPB193). Palladium catalysis, without ligation of the catalyst to triphenylphosphine ligand, was used for the alkenylation of 5-iodopyrimidines with ethyl acrylate (81H965).

Methoxy- or methylthio-5-iodopyrimidines (9) are effectively coupled with methyl acrylate to form the product (10). Reaction of the 5-bromo analog is slower, and is sensitive to vicinal interaction; in 4,6-disubstituted pyrimidines, most of the substrate was unreacted (only a 10% yield) (86S555). A free amino group in the 4-position (11) is tolerated in the preparation of the alkenylated product (12) (82CPB2410).

Alkenylation (14) of the 5-bromo derivative was also slow in reactions with methyl vinyl ketone. The main coupling product (15) from the reaction with 5-iodopyrimidines (13) was saturated. The reaction path for saturation



SCHEME 3

must involve cleavage of the Pd—C bond in the intermediate complex without Ph—H elimination (88S771).

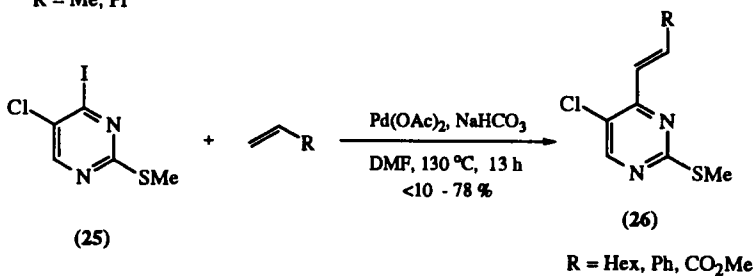
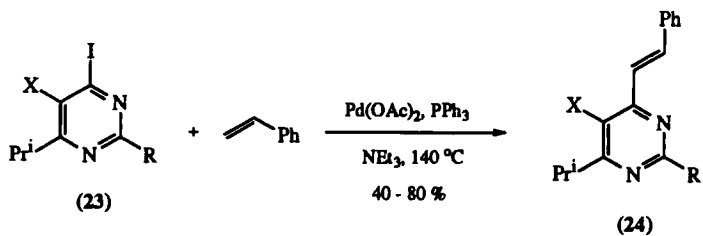
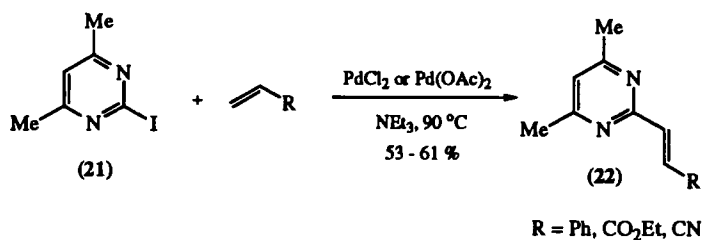
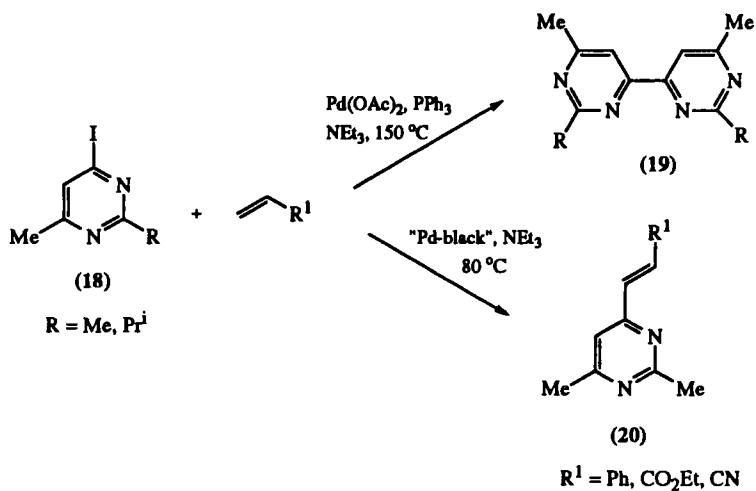
A triflyloxy substituent may replace the iodo substituent in an efficient approach to carbon-carbon bond formation in alkenes and arenes. Applied to pyrimidine chemistry, it has been found that cross-coupling of 5-triflyloxyuracil with alkenes and alkynes leads to 5-alkenylated and 5-alkynylated uracils (87H355). Similarly *N*-methyl- or *N,N'*-dimethylpyrimidin-5-yl triflate (**16**) reacts with styrene, acetonitrile, methyl acrylate, or methyl vinyl ketone to form the alkenylated products (**17**) (87H355).

Alkenylation of 4-iodopyrimidines, in contrast to the 5-iodopyrimidines, is difficult. Under the relatively severe reaction conditions required for cross-coupling with 4-iodopyrimidines, formation of 4,4'-bipyrimidines (**19**) becomes a major pathway (Scheme 4). In the absence of alkenes homo-coupling (160°C) is almost quantitative (79CPB193). In the absence of triphenylphosphine ligation, however, the 4-iodopyrimidine (**18**) is readily alkenylated in reactions with ethyl acetate and Pd-black as catalyst. With acrylonitrile or styrene, a mixture of alkenylated (**20**) and homo-coupled (**19**) products results (81H965; 82CPB3647).

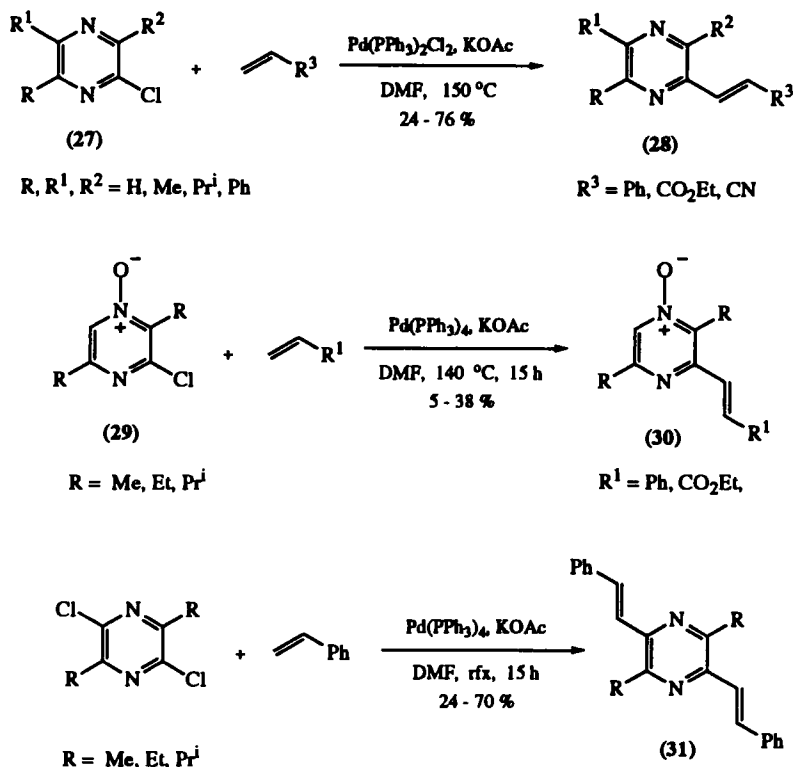
The 2-iodo derivative (**21**) is even less reactive than its 4-isomer. No alkenylation was observed with phosphine-ligated Pd (79CPB193; 82CPB3647), but moderate yields of 2-alkenylated pyrimidines (**22**) are produced in the absence of triphenylphosphine (81H965).

Coupling in the 4-position is reported to be promoted by 5-substituents (I, Br, Cl, OEt, Et). In 4,5-diiodopyrimidines (**23**), it is the 4-iodo substituent that is displaced (**24**) with triphenylphosphine-ligated Pd (79H383). No phosphine ligand was used in the alkenylation of the 5-chloro-4-iodopyrimidine (**25**) with styrene or methyl acrylate. Sodium bicarbonate is a suitable base in this reaction. Exclusive coupling takes place in the 4-position to give product (**26**) in the *trans* configuration. With hexene as substrate, less than 10% alkenylated pyrimidine was formed, which indicates that the usefulness of the alkenylation reaction is limited to polarizable double bonds, preferably containing an electron-withdrawing substituent [87ACSA(B)712]. A more general method (see below) for vinylation of halogeno- or triflyloxyheterocycles consists in coupling a halogeno- or triflyloxyheterocycle with a vinylstannane under the influence of Pd-catalysis (93ACSA102).

c. *Pyrazines*. All ring carbons in pyrazine can be considered electrophilic, and hence chlorine substituents are replaceable in alkenylation reactions (86JHC1481). The 2-chloropyrazines (**27**) react in moderate yields with styrene, ethyl acrylate, and acrylonitrile (Scheme 5). The



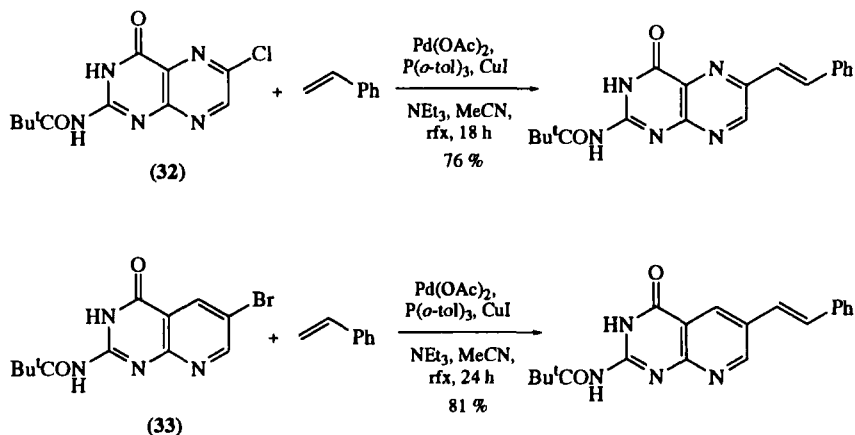
SCHEME 4



SCHEME 5

products (28) from styrene and acrylates have the (*E*)-configuration. With acrylonitrile, however, the stereochemical ratio varied from 3:1 to 2:1 (86JHC1481). Corresponding coupling reactions with the *N*-oxides (29) give coupling products (30) in yields on the order 30%. With 2,5-dichloropyrazines as substrate, dialkenylation (31) results in variable yields, with 24% for the 3,6-dimethyl derivative (86JHC1481).

d. *Pteridine and 1,3,8-Triazanaphthalene*. The alkenylation protocol has been used to effect indirect formylation in the 6-position of the pteridine ring system (Scheme 6). The 6-chloride (32) is alkenylated with styrene and the coupled product is ozonized; hydrolysis yields the 6-formylpterine (87SC1865). 5-Deazapterine (33) is formylated in the same manner. The halogen in this molecule is in the 6-position and therefore must be a bromine (or iodine) in order to effect a smooth reaction (88SC1187).



SCHEME 6

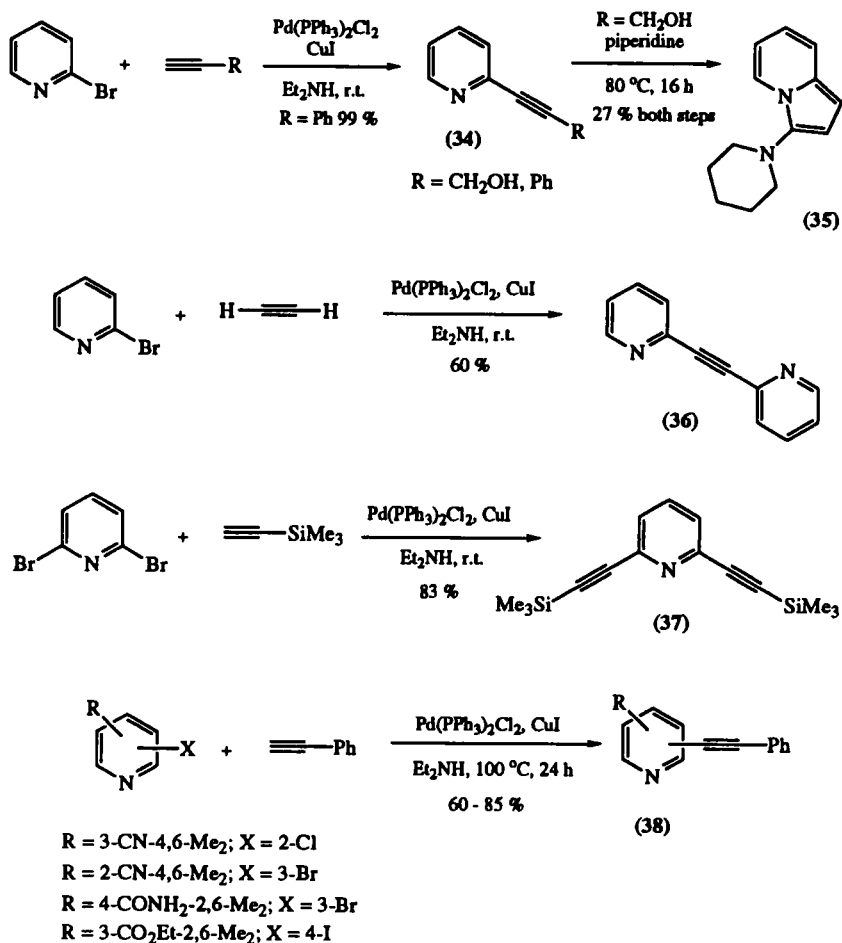
B. ALKYNYLATION BY PALLADIUM CATALYSIS

1. General

Terminal alkynes can be coupled directly to aryl, heteroaryl, and vinyl halides or triflates in the presence of a Pd-catalyst and a base, which frequently is an amine acting both as solvent and as scavenger for the respective acid formed in the reaction. The mechanism appears to involve oxidative addition of the sp^2 -halide or triflate to Pd(0), followed by alkynylation of the intermediate organopalladium complex and reductive elimination of the substituted alkyne. Copper(I) iodide is a particular effective cocatalyst, allowing the reaction to proceed at room temperature (91MI2).

2. Alkynylation Reactions

a. *Pyridines*. The initial work was on 2-bromopyridine, which was alkynylated (34) with phenylacetylene in high yield (Scheme 7). When propargyl alcohol was coupled without protection of the hydroxyl group, the yield was relatively low (27%). Acetylene itself is coupled on both carbons to give bis(2-pyridyl)acetylene (36) (75TL4467). When monocoupling is desirable, a monoprotected acetylene is used as substrate; silyl protection is suitable. 2,6-Dibromopyridine can be dialkenylated (37) by trimethylsilylacetylene (80S627).

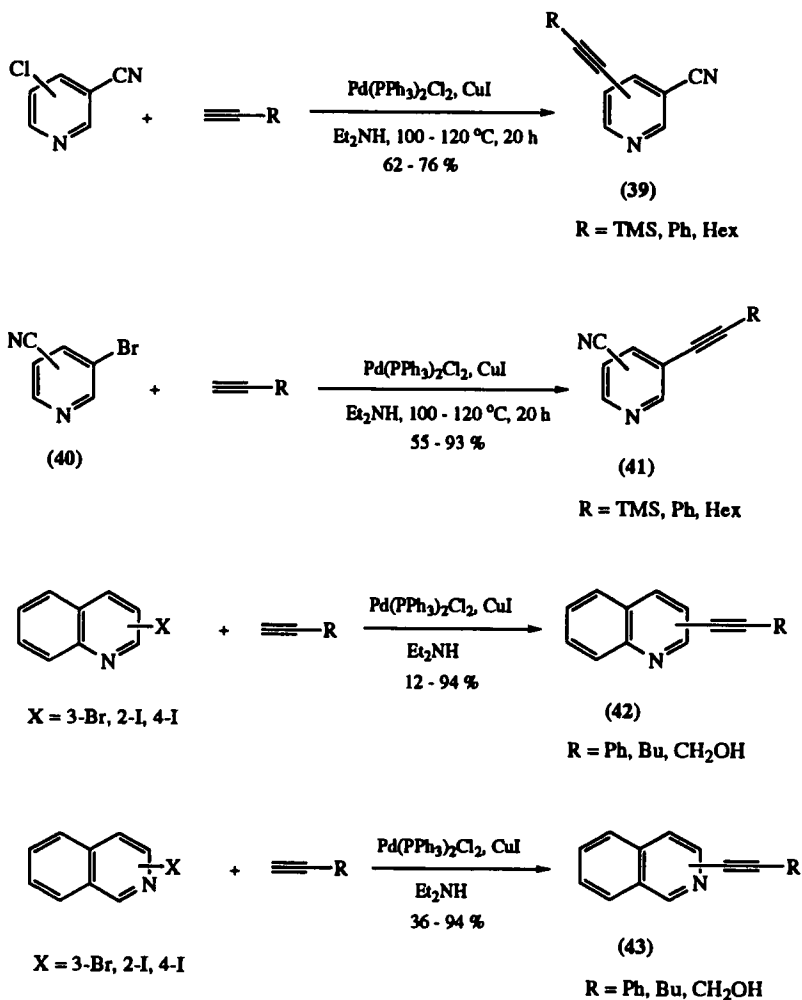


SCHEME 7

When the reaction with propargyl alcohol is run in an amine solution at elevated temperature, the alkynylated product first formed is further transformed by a cyclization reaction with the pyridine nitrogen; 3-piperidinoindolizine (35) is formed (36% yield) in piperidine at 80°C . Corresponding cyclization products result from the reaction with 1-bromoisoquinoline or 2-bromoquinoline with propargyl alcohol (80BCJ3273). Alkynylation (38) of 2-chloro-, 3-bromo-, and 4-iodopyrimidines, which are vicinally substituted by a cyano, carbamoyl, or ethoxycarbonyl group, has been effected with phenylacetylene by heating the

reactants together in triethylamine. The products (38) are useful intermediates in syntheses of naphthyridines (85CPB626).

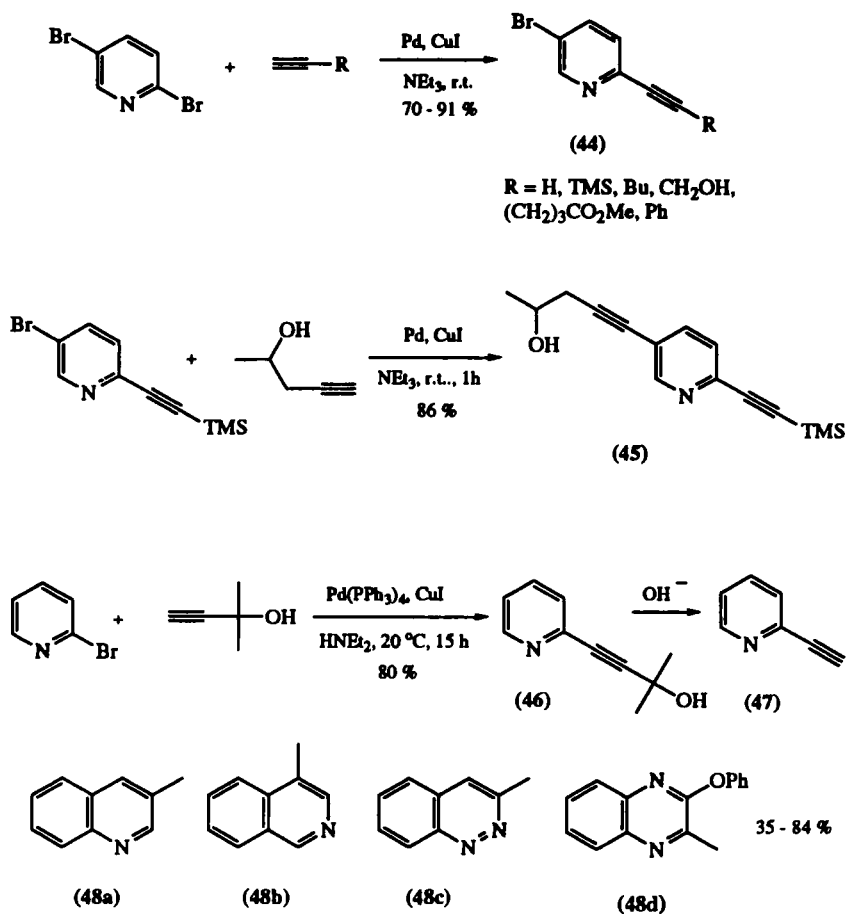
The alkynylation (39) of 2- and 4-chloropyridine-3-carbonitriles has been effected by phenylacetylene or 1-hexyne (Scheme 8). Alkynylation in the 3-position (41) requires a 3-bromo substrate (40) (85CPB626; 88CPB1890). The fused pyridines—quinoline, isoquinoline, and acridine—have been alkynylated in all positions in the heterocyclic ring (42, 43) (79CPB270).



SCHEME 8

2,5-Dibromopyridine reacts regioselectively in the electrophilic 2-position to give 2-alkynyl-5-bromopyridines (**44**) (Scheme 9), which are useful precursors for other 2,5-disubstituted pyridines. The (trimethylsilyl)alkynyl derivative (**44**) has been reacted further with 4-pentyn-2-ol under essentially the same conditions to form the dialkynylated product (**45**) (88JOC386).

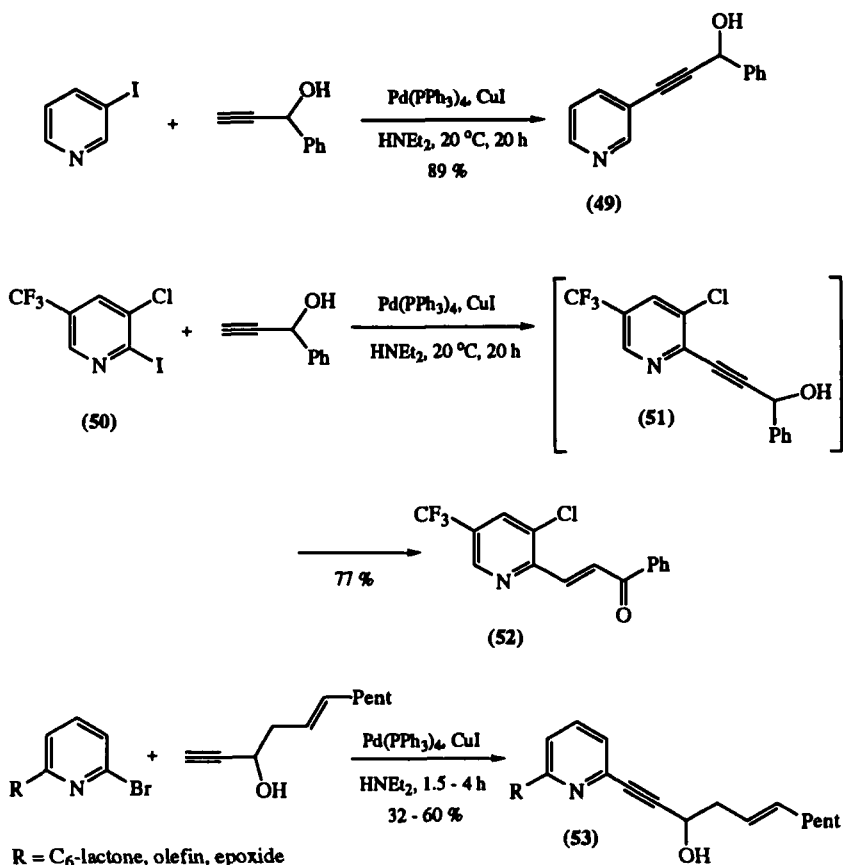
The trimethylsilyl (TMS) group from the acetylenic reagent is retained in the alkenylated product. Deprotection to a derivative with a free acetylenic group is achieved by dilute aqueous methanolic KOH. In an alternative method for acetylene protection, 2-methyl-3-butyne-2-ol has been used.



SCHEME 9

Alkynylation of 2-bromopyridine with this alkynol according to the standard protocol gives the coupling product (46). Bromo derivatives of quino-line, isoquinoline, cinnoline, and quinoxalines give the corresponding alkynyl compounds (48) in moderate to good yields. Cleavage of the alkynol (46) by base to the free alkyne (47) expels acetone (81S364).

Phenyl-substituted propargyl alcohol couples with 3-iodopyridine to furnish (49) (Scheme 10). On reaction of the 2-iodopyridine (50), however, it was found that the initial alkynylation product (51) rearranged to form the corresponding chalcone (52). The same rearrangement occurs in pyrimidines when the iodine is located in an electrophilic position. In reactions with the corresponding methylpropargyl alcohol, the reaction stops after

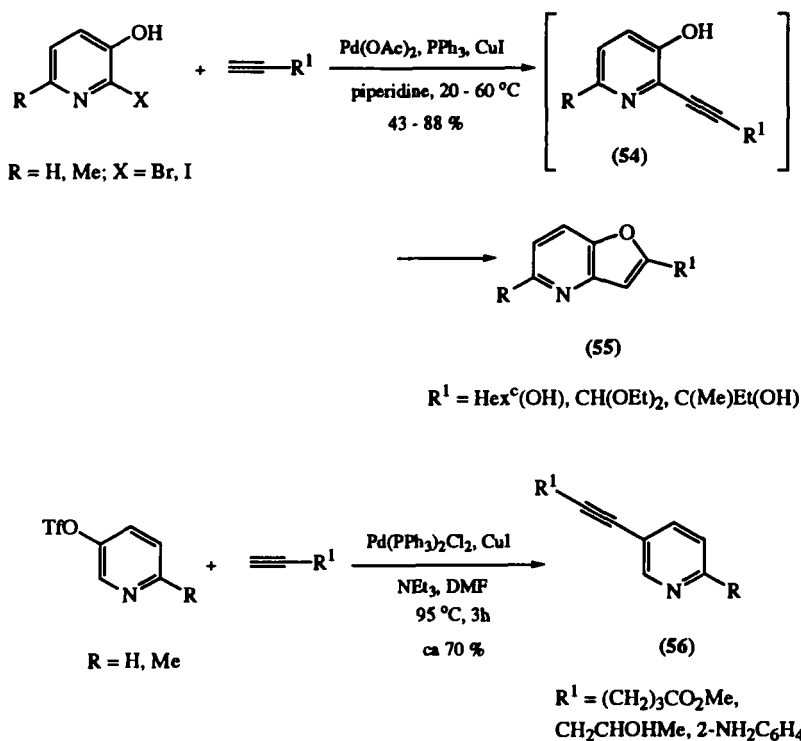


SCHEME 10

alkynylation (91SL115). The alkynylation reaction has been used as a key step in the synthesis of leukotriene B₄-antagonists; an allylpropargyl alcohol substrate was used to prepare the en-yne derivative (53) (88TL143).

After alkynylation (54), 2-bromo- or 2-iodo-3-hydroxypyridine is cyclized by the hydroxy group to form furo[3,2-*b*]pyridines (55) (Scheme 11). Benzofurans are formed similarly. Protection of the hydroxyl group in propargyl alcohol or its substituted derivatives is not necessary (86S749). This reaction sequence can also be used to prepare the corresponding furo[2,3-*d*]pyrimidin-2-ones (see below).

Pyridyl triflates in the benzenoid 3-position readily couple with terminal acetylenes (88JOC386). When the phenylacetylene is substituted in the phenyl ring by an *o*-amino group, the alkynylated product (56) can be cyclized by Pd(II)-catalysis to an indole, in this case to 2-(3-pyridyl)indole (89TL2581).



SCHEME 11

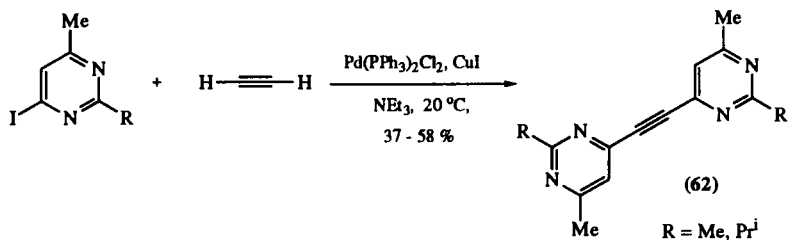
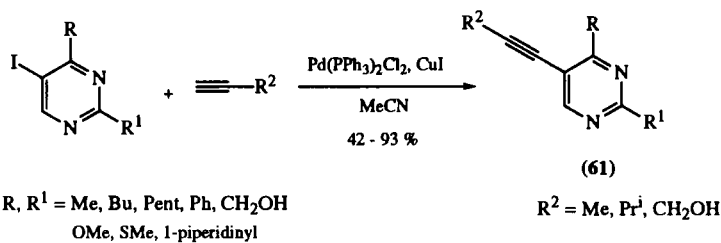
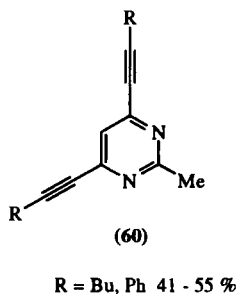
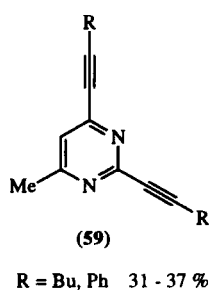
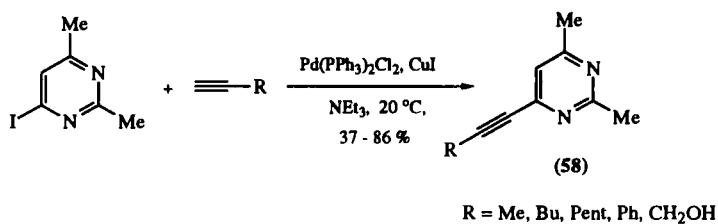
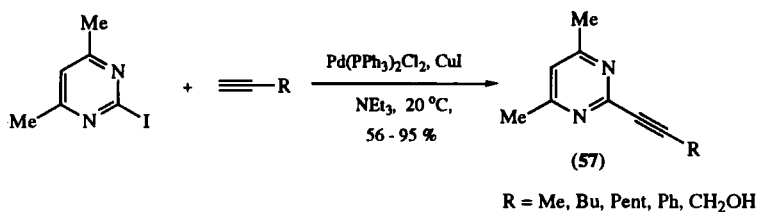
b. *Pyrimidines*. Reports on the alkynylation of pyrimidines go back to 1978. 2-Iodo- or 4-iodopyrimidine was readily alkynylated (**57**, **58**) (Scheme 12). Unprotected propargyl alcohol gives a modest yield of alkynylated products (**57**, **58**). Selectivity could not be effected between the slightly differently activated 2- and 4-positions in 2,4-diiodopyrimidines; the latter was dialkynylated (**59**). 4,6-Diiodopyrimidine also reacts with dialkynylation (**60**) (78H271). Methoxy-, methylthio-, or piperidino-substituted iodo-pyrimidines react in the same manner (**61**) as the methyl derivatives (78CPB3843). 2-Chloro- and 4-chloropyrimidines can be used as substrates, although their reactivity is inferior to that of 2- and 4-iodopyrimidines; reflux conditions in triethylamine are used for the chloro derivatives, and room temperature for the iodo derivatives. In the benzenoid 5-position the halogen must be either a bromine or iodine atom for the alkynylation reaction to proceed (78CPB3843). Acetylene coupling with 4-iodopyrimidines gives disubstituted alkyne products (**62**) (78CPB3843).

5-Bromopyrimidines are alkynylated in the 5-position (**63**) using standard catalyst composition and heating (Scheme 13). In the electrophilic 4-position, the chloro derivative, additionally activated by the 5-carbethoxy group, can be alkynylated (**64**) according to the standard protocol (82CPB2410). In the 4-chloro-5-iodopyrimidine (**65**), the iodine in the 5-position is selectively displaced in the alkynylation (**66**). In the 4-iodo-5-chloropyrimidine (**67**), coupling is in the 4-position (**68**).

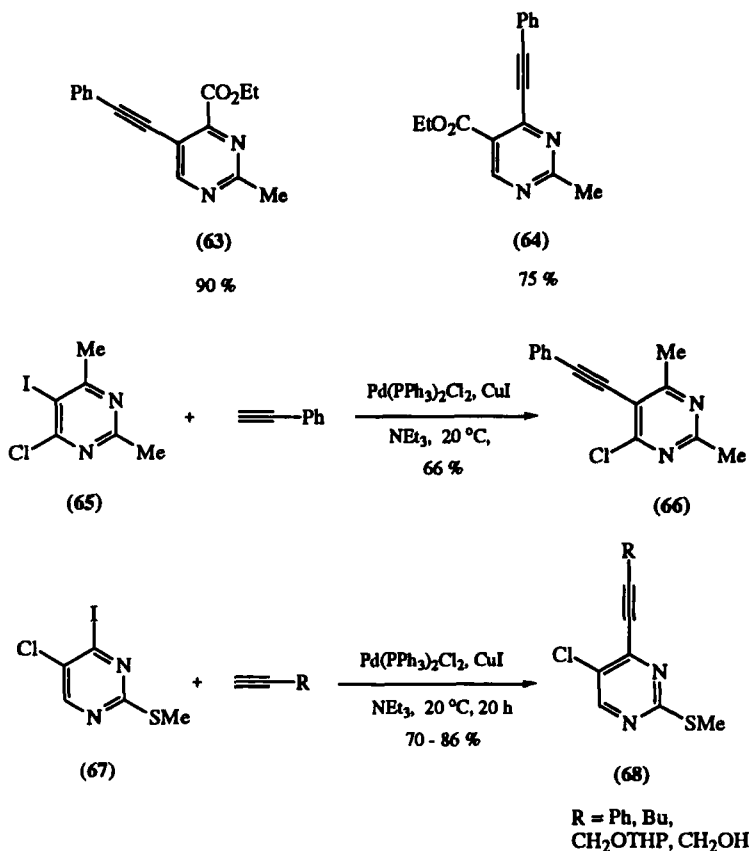
In coupling with the silyl-protected 2-pyrimidinone (**69**) (Scheme 14), hydrolysis of the silyl ether function during the reaction is prevented by hexamethyldisilazane (HMDS), which is added to trap any water in the reaction mixture; high yields of the *O*-protected alkyne (**70**) result [86ACSA(B)381]. The 5-iodopyrimidin-4-one (**71**) is alkynylated (**72**) according to the standard protocol at 50°C. The product reacts further on heating and is cyclized to the fused furo[2,3-*d*]pyrimidine (**73**) (82CPB2417).

In yet another example, 5-iodo-1-methyluracil is alkynylated (**74**) by 1-hexyne. The minor product (9%) from the reaction is furo[2,3-*d*]pyrimidin-6-one (**75**). The latter arises from (**74**) by a cyclization reaction. The cyclization was effected by heating the alkynylated product (**74**) with CuI/NEt₃/MeOH, with yield 92% of the furopyrimidine (**75**) (81TL421; 83JOC1854). This reaction constitutes a simple and general method for the preparation of furo[2,3-*d*]azines.

c. *Pyridazine and Pyrazine*. Coupling in pyridazines is illustrated by 3-chloro-4-cyanopyridazine (Scheme 15). The chlorine is situated in an electrophilic azine position and is further activated by the vicinal cyano group. The alkynylated product (**76**) is formed from phenylacetylene under standard conditions (88M751).



SCHEME 12

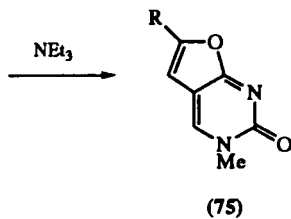
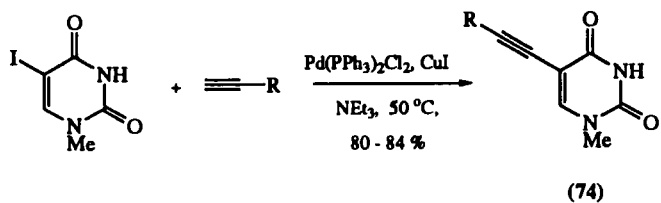
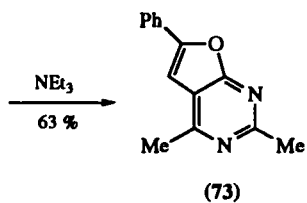
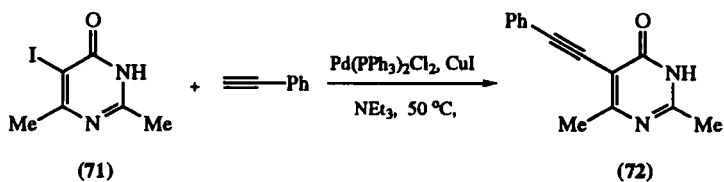
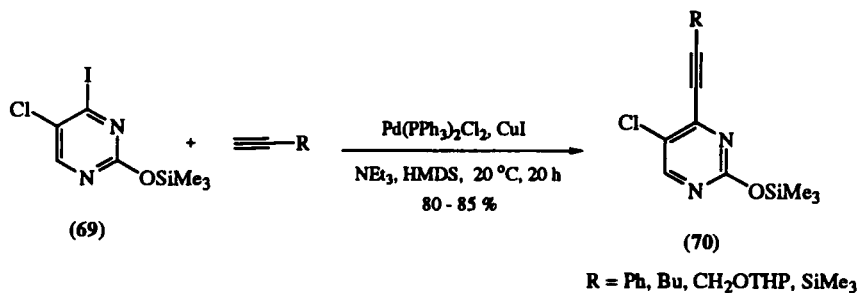


SCHEME 13

In pyrazines all positions are electrophilic; a chlorine is replaceable by alkynylation (77) using the standard coupling protocol and heating at 100°C. 2,5-Dichloropyrazines are also dialkynylated (78).

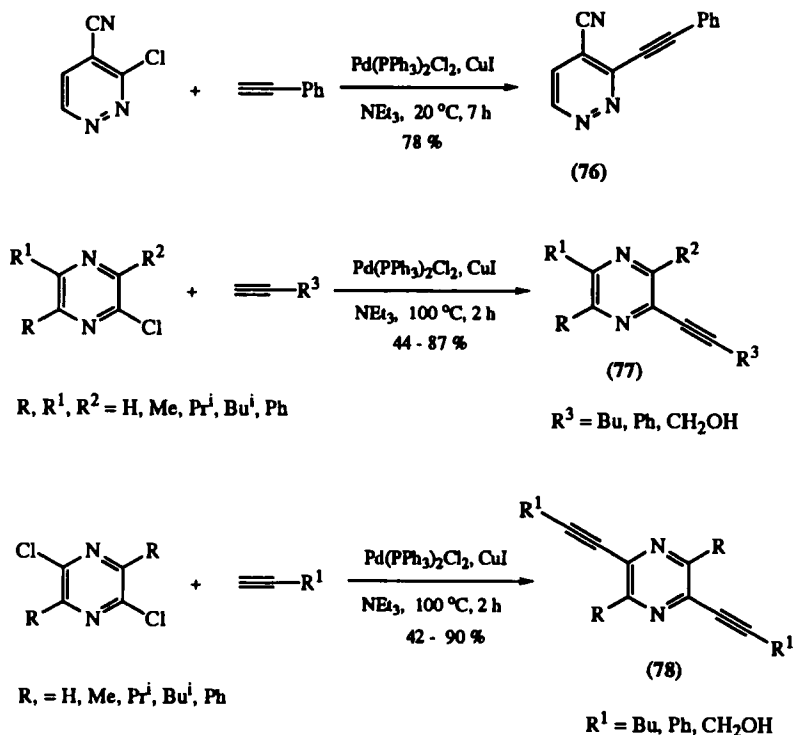
Reaction of the 4-*N*-oxide of 2-chloropyrazine proceeds without interference from the *N*-oxide function to give (79) (Scheme 16). In the 1-*N*-oxide (80), however, alkynylation is difficult, and the reaction failed in most cases. From phenylacetylene 18% of the alkynylated product (81) was isolated (86CPB1447).

2-Amino-5-bromo-3-cyanopyrazine is an intermediate in the construction of pteridines. Before forming the fused pyrimidine ring, the pyrazine is alkynylated in the 5-position (82) in moderate to good yields (87JOC3997; 88JOC35).



R = Bu, CH₂CH₂O-*p*-tol

SCHEME 14

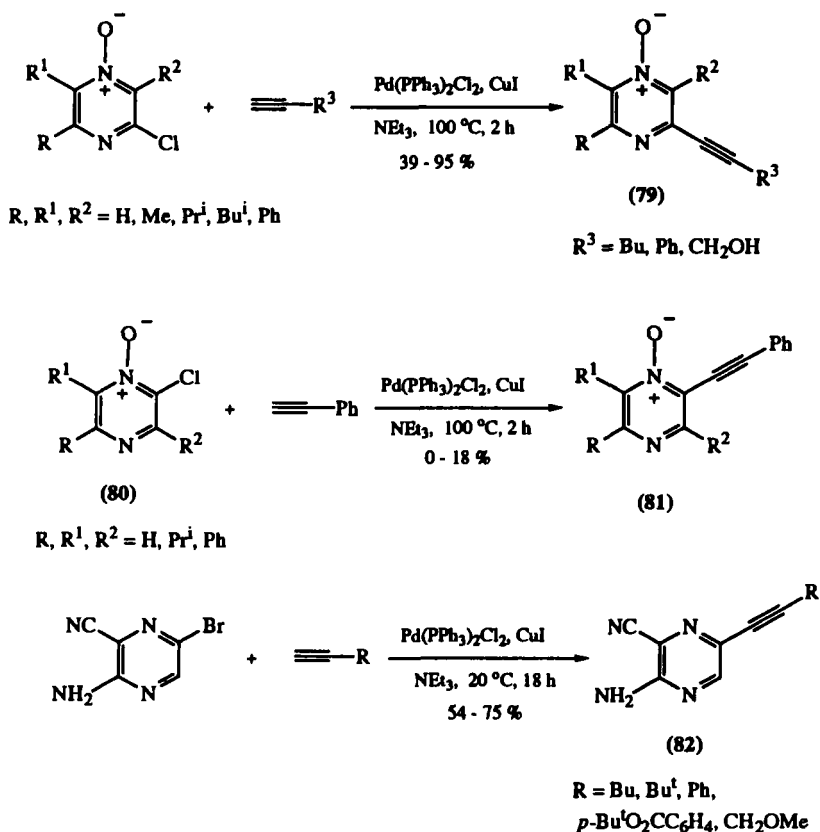


SCHEME 15

d. *Quinazoline*. In 4-chloroquinazoline the halogen is situated in the electrophilic 4-position and is readily replaced by an alkynyl substituent (83) (Scheme 17) (78CPB3843).

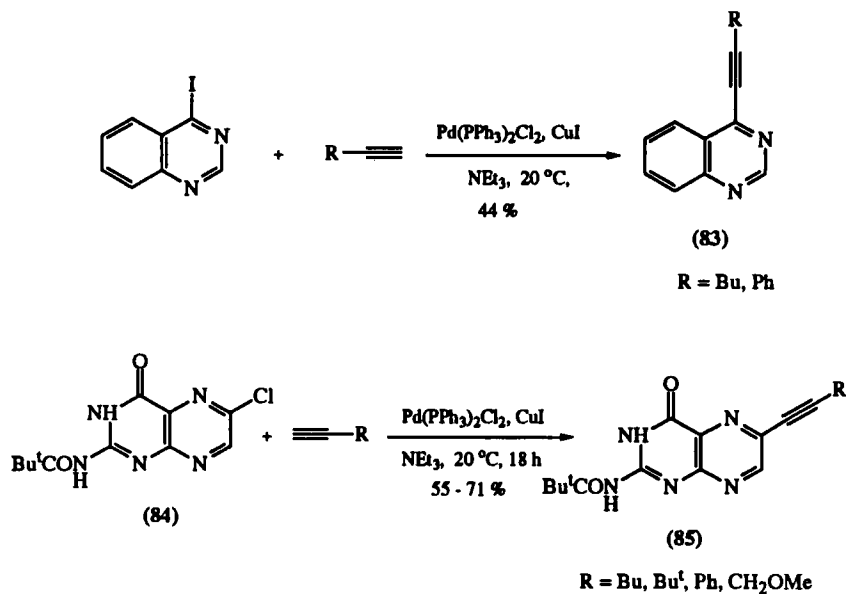
e. *Pteridine*. The chlorine in the activated 6-position in pteridine (84) can be replaced by alkynylation (85) using the standard coupling protocol. 6-Chloropterine (84) was initially pivaloylated to enhance solubility in organic solvents (87JOC3997).

f. *Triazine*. 1,2,4-Triazines show the usual higher reactivity of an iodo compared to a chloro substituent in the 5-position (Scheme 18). The standard coupling protocol at room temperature results in high product formation (86) from iodo substrates. The yields are significantly lower from the chloro substrates. High coupling efficiency is also seen for the 3-iodotriazine (87) (84H2245).

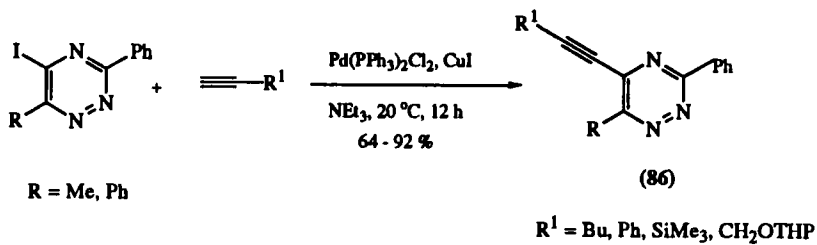


SCHEME 16

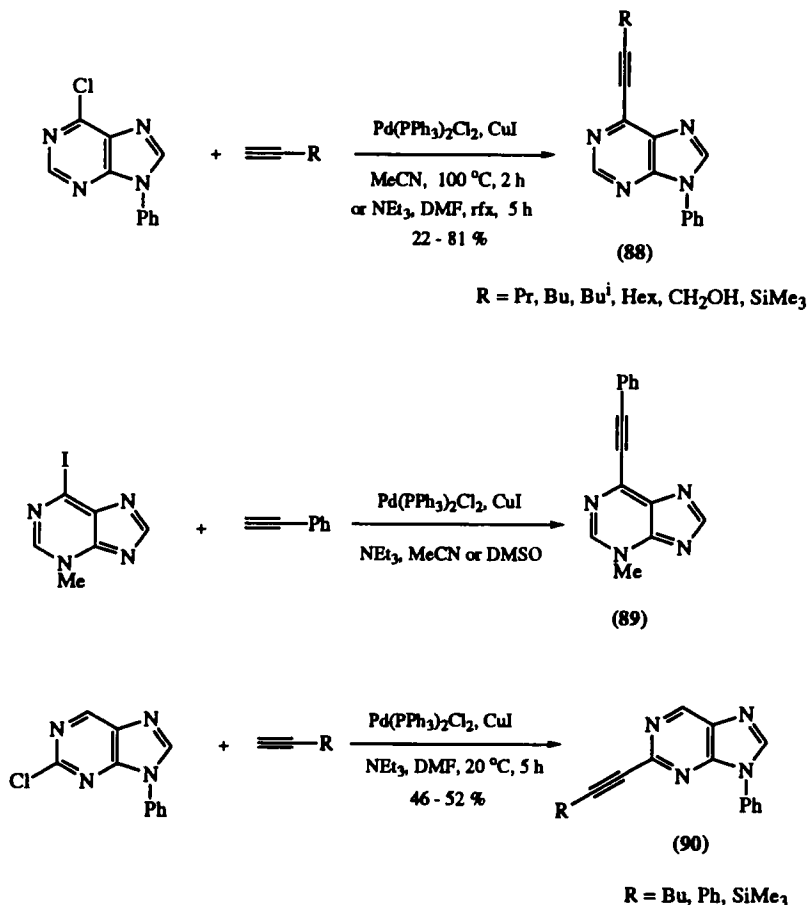
g. *Purine*. The purine 6-position is strongly electrophilic; a chlorine in this position can be substituted under the conditions of alkynylation (Scheme 19). 6-Chloropurine itself gives modest to moderate yields of coupling products, but protection of the purine by *N*-9 acetylation doubles the yields of alkynylated product in some cases (86ABC2377). Similarly, 6-chloro-9-phenylpurine undergoes alkynylation (88) by heating in dimethylformamide (DMF), whereas the 6-iodopurine can be coupled at room temperature with significant improvement in yields of alkynylated products (88) (88CPB1935). 6-Iodo-3-malkylpurine is also readily alkynylated (89) without heating (90H1155). Coupling of 2-chloro-9-phenylpurine with alkynes can be used to prepare alkynylated products (90) (88CPB1935).



SCHEME 17

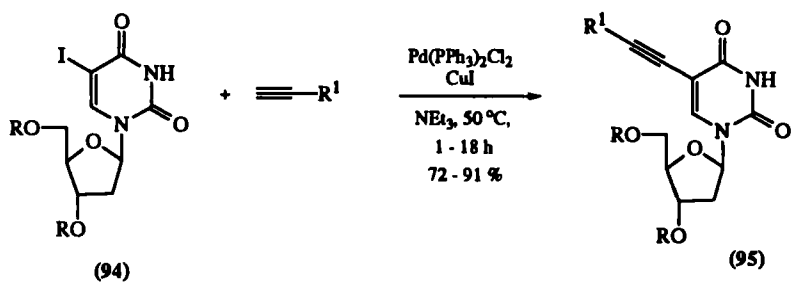
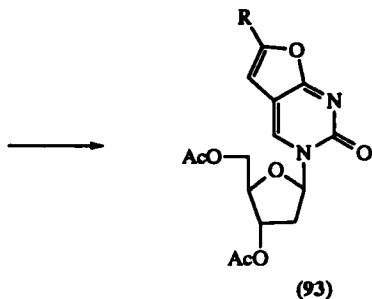
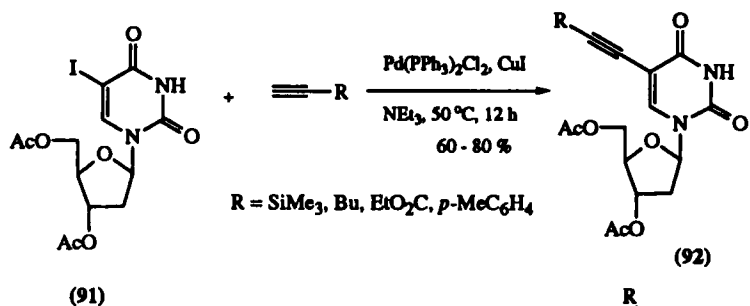


SCHEME 18



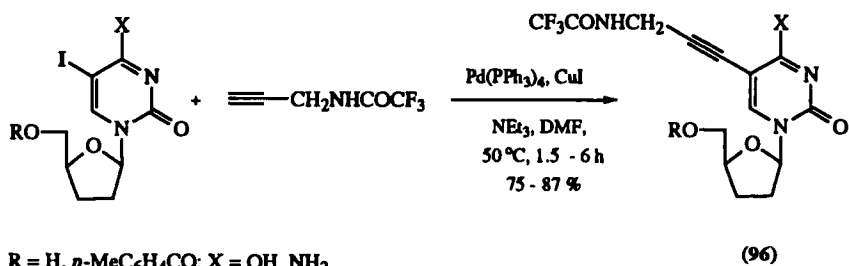
SCHEME 19

h. *Pyrimidine Nucleosides*. Alkynylation of nucleosides has been used to introduce carbosubstituents into the heterocyclic base (Scheme 20). Coupling of 5-iodo-3',5'-di-*O*-acetyl-2'-deoxyuridine (**91**) with (trimethylsilyl)acetylene yields the alkynylated product (**92**) in high yield. Under the same reaction conditions with hexyne and variously protected butyn-4-ols, the initial product is cyclized to the furo[2,3-*d*]pyrimidin-6-one nucleoside (**93**), which is the major product (83JOC1854). The cyclization reaction is sensitive to the nature of the substituents and substrates; protection by the *p*-toluyl group in the 2'-deoxyuridine (**94**) gives high yield of the alkynylated products (**95**) (81TL421; 83JOC1854).



$\text{R} = p\text{-MeC}_6\text{H}_4\text{CO}$

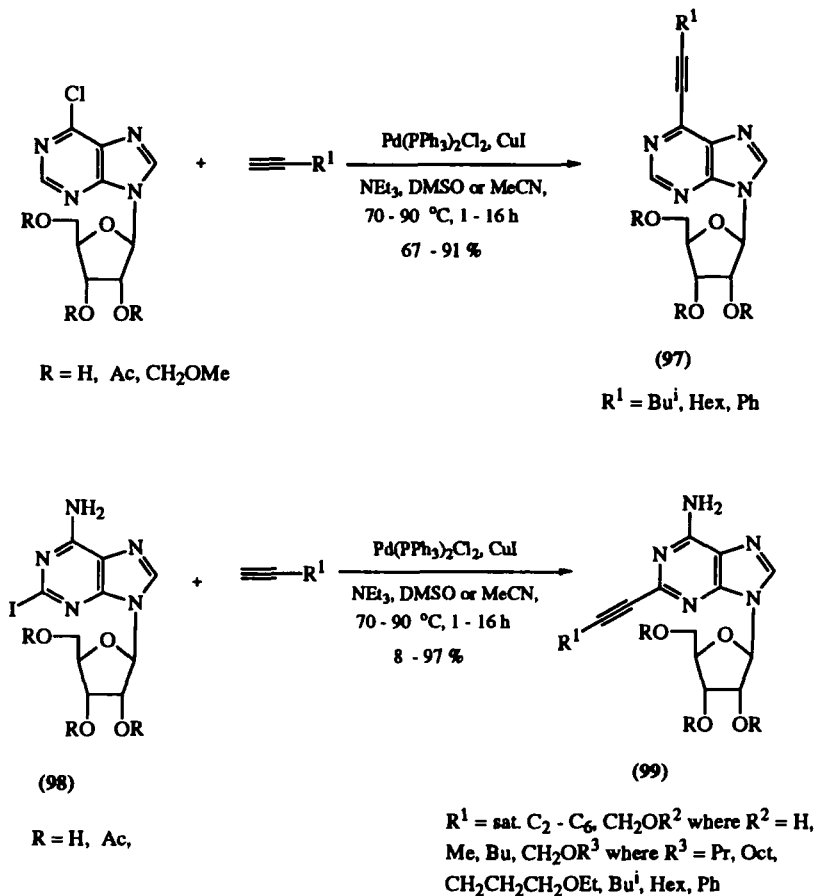
$\text{R}^1 = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{Bu}^t, \text{Pent}, \text{Ph}, \text{SiMe}_3$
 $\text{CH}_2\text{CH}_2\text{OR}^2$ where $\text{R}^2 = \text{H}, \text{THP}, p\text{-tol}, \text{Ts}$



SCHEME 20

Propargylic amines undergo rapid coupling with 5-iodouracil derivatives. The initial coupling products are susceptible to secondary cyclization reactions with the vicinal amino group, resulting in low to moderate yields of 5-alkynyluracil nucleosides (**96**). Higher yields of alkynylated products (**96**) are obtained with $\text{Pd}(\text{PPh}_3)_4$ than with $\text{PdCl}_2(\text{PPh}_3)_2$ in DMF (90TL3731).

i. *Purine Nucleosides.* 6-Chloro-9-(β -D-ribofuranosyl)purine is readily alkynylated (**97**) by the standard protocol in dimethyl sulfoxide (DMSO) or acetonitrile with some heating (Scheme 21). The product yield is in-



SCHEME 21

creased (~10%) when the hydroxyl groups of the sugar are protected, and the yields are generally high (82MI1).

Coupling in the purine 2-position is demonstrated for 2-iodoadenosine (98). The coupling to form (99) proceeds very readily in most cases with the standard protocol in DMF at 80°C, except for the three butyn-4-ols and the pentyn-5-ol whose yields were in the range 8–42% (85CPB1766; 92JMC241).

III. Cross-Coupling by Metal Substitution

A. ORGANOTIN COMPOUNDS (STANNANES)

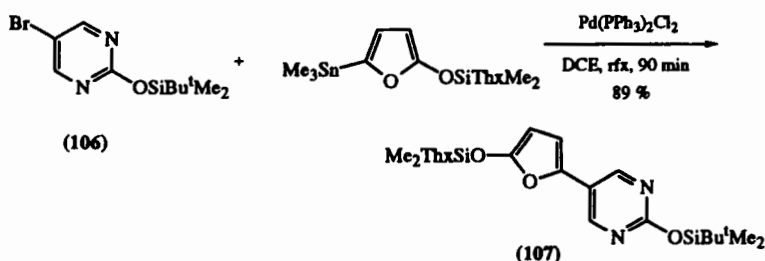
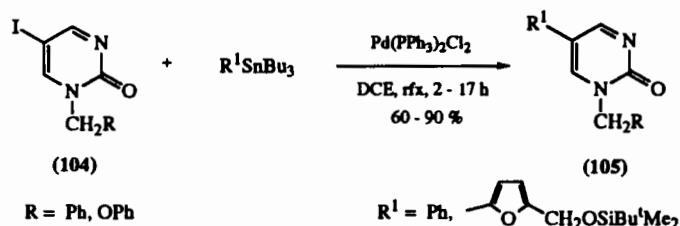
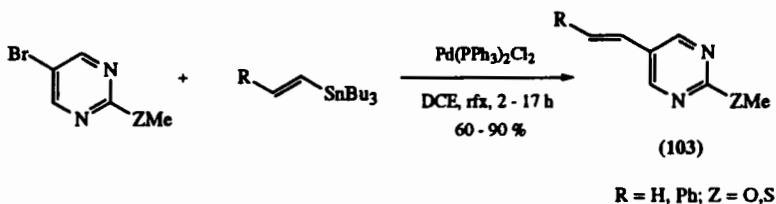
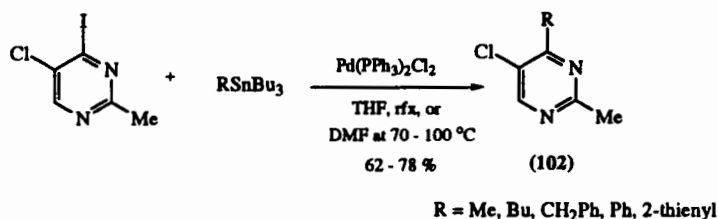
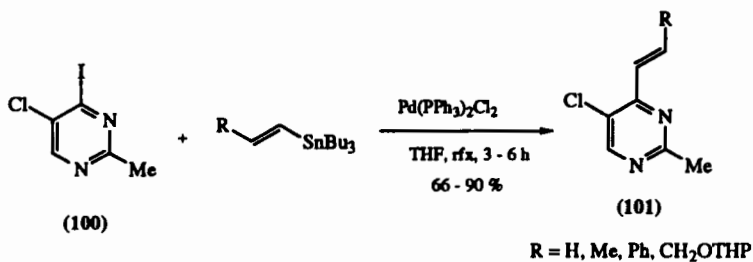
1. General

Organotin compounds have become widely used reagents in metal-catalyzed cross-coupling reactions because of their ease of preparation and handling as well as their high reactivity in the presence of Pd-catalysts (86AG504; 87MI1; 92S803). They are, however, toxic.

2. Halogeno- and Triflyloxy-azines

a. *Pyrimidines*. Extensive application of stannane chemistry to carbon-carbon bond formation in heterocycles has been reported (Scheme 22). Coupling reactions between the 5-chloro-4-iodopyrimidine (100) and substituted alkenyltributylstannanes are stereospecific in alkene reagents with retention of the stereochemistry (101). Coupling takes place exclusively in the activated 4-iodo position. The reaction with alkenylstannanes is run under reflux in tetrahydrofuran (THF). Under these conditions *cis*-propenyltributylstannane is slightly isomerized (10%) to the *trans* form. The *trans* derivative is formed exclusively in a reaction with allyltributylstannane. The allylated product may form initially, but it is isomerized to the product with a double bond conjugated to the electronegative heterocycle [87ACSA(B)712]. Phenyltributylstannane gives the 4-phenylation product (102). The coupling of aryl bromides with stannanes is promoted by electron-withdrawing substituents in the aryl ring. This has been demonstrated for the reaction between styryltributylstannane and an equimolar mixture of the 4-iodopyrimidine (100) and iodobenzene; the coupling product arose exclusively from the 4-iodopyrimidine [87ACSA(B)712].

sp^3 -Hybridized carbon attached directly to the metal is less reactive than sp^2 - or sp -hybridized carbon in Pd-catalyzed reactions. Tetramethyl- or tetrabutylstannane can be used for the preparation of methyl and butyl



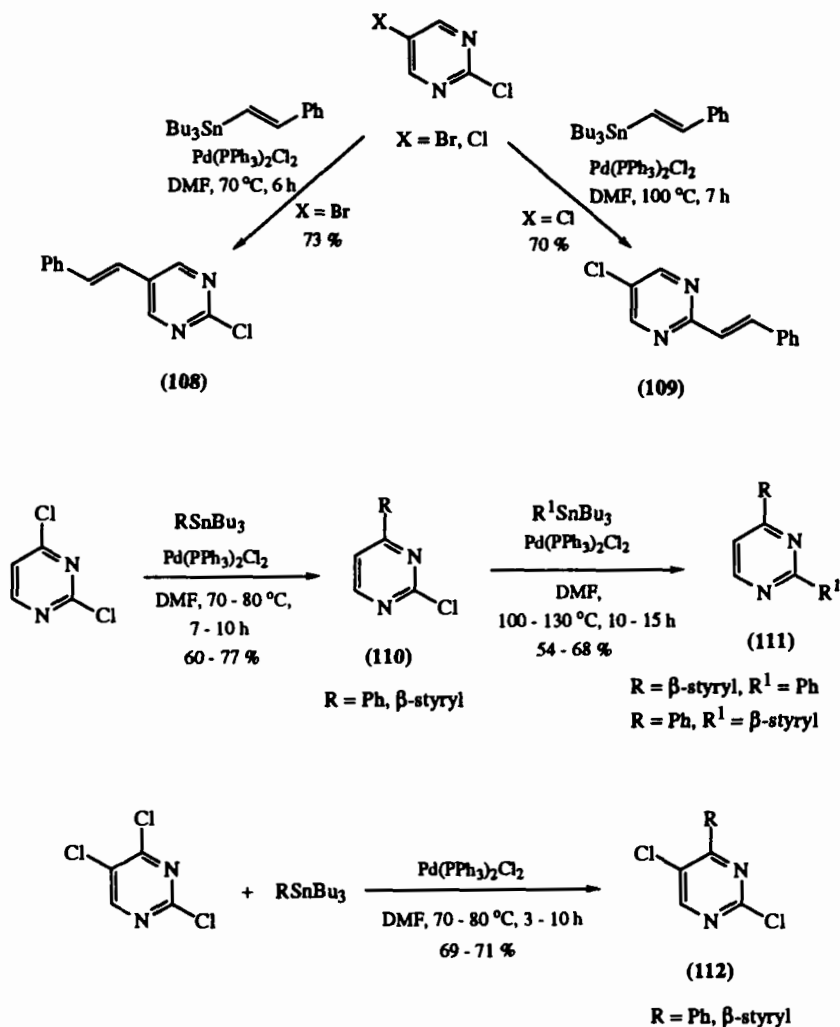
SCHEME 22

derivatives, but these reactions require heating in DMF at elevated temperatures for a long time. The reactivity is enhanced when the sp^3 -hybridized carbon carries an electronegative group. Therefore, in the reaction between benzyltributylstannane and iodopyrimidine, it is the benzyl group that is transferred to the pyrimidine to form (102). With allyltributylstannane the product is the 4-*trans*-propenylpyrimidine (101) [87ACSA(B)712]. Alkylzinc reagents or alkylaluminum reagents (see below) may be a better choice for simple alkylation reactions.

5-Bromopyrimidines give 5-alkenyl derivatives (103) when coupled with alkenylstannanes [88ACSA(B)455]. The 5-iodo-2-pyrimidinone (104) can be alkynylated (105) with phenylethynylstannane, and heteroarylated with 2-stannyl derivatives of 5-hydroxymethylfuran (93ACSA102; 94ACSA279). A bulky silyl group is used for protection of the alcoholic function in the hydroxymethylfuran. Bulky silyl groups can also be used for protection and solubilization of pyrimidinones (106). In the coupling product (107), where both the alcoholic and the phenolic hydroxyl groups are silyl-protected, selective cleavage of the phenolic silyl ether is effected with acetic acid (94ACSA279).

The coupling reaction between aryl halides and organostannanes generally requires the arene to be a bromo or iodo derivative; replacement of a chloro substituent requires the presence of a strongly electron-withdrawing group (86AG504; 86S564; 87JOC422). In π -deficient heteroarenes, a chloro substituent is readily introduced into electrophilically activated positions from hydroxyl groups via well-established procedures and, to some extent, from amino groups. The less readily available bromo and iodo derivatives are often prepared from the chlorides by halogen exchange reactions. It was therefore a significant improvement when it was gradually established that a chlorine in an electrophilic azine position could be replaced by a carbosubstituent in Pd-mediated catalytic reactions. This methodology permits metal-catalyzed introduction of carbosubstituents into all π -electron deficient heteroarenes where the corresponding chloro compounds are readily available, e.g., in purines and pteridines.

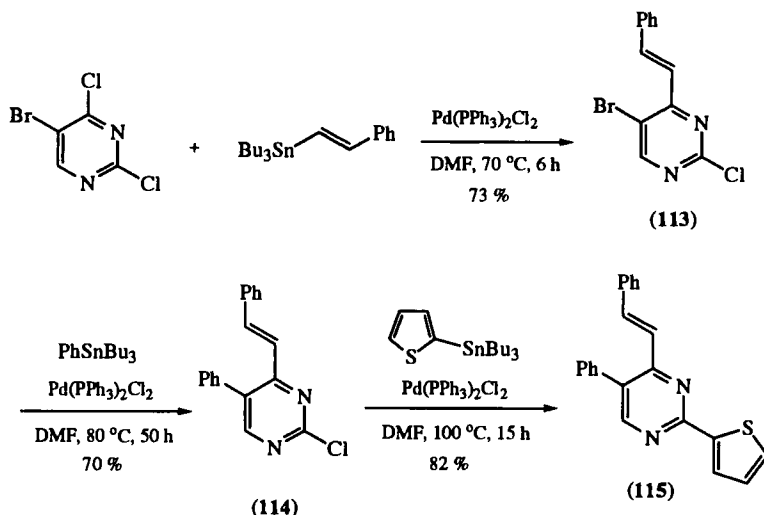
Since chloro substituents in the benzenoid pyrimidine 5-position will not normally react with a stannane, the reaction between 2,5-dichloropyrimidine and styryltributylstannane is specific for the activated 2-position; 5-bromo-2-chloropyrimidine is coupled with selective substitution of bromine in the 5-position (108). The 2-chlorine can subsequently be substituted [89ACSA(B)62]. In reactions of 2,4-dichloropyrimidine with β -styryl- or phenyltributylstannane the carbosubstituent is selectively introduced into the 4-position (110) [89ACSA(B)62]. The same regioselectivity is observed for Ni-catalyzed coupling with organomagnesium reagents (see below), and the regioselectivity corresponds to the relative reactivity



SCHEME 23

of pyrimidine toward nucleophiles. A second carbo substituent can subsequently be substituted into the 2-position (111). In 2,4,6-trichloropyrimidine the chlorine in the 4-position is replaced selectively under the conditions for monocoupling (112).

A good demonstration of the regio- and chemoselectivity in these reactions is provided by the stepwise introduction of three different carbo substituents into 5-bromo-2,4-dichloropyrimidine (Scheme 24). Initial styryla-



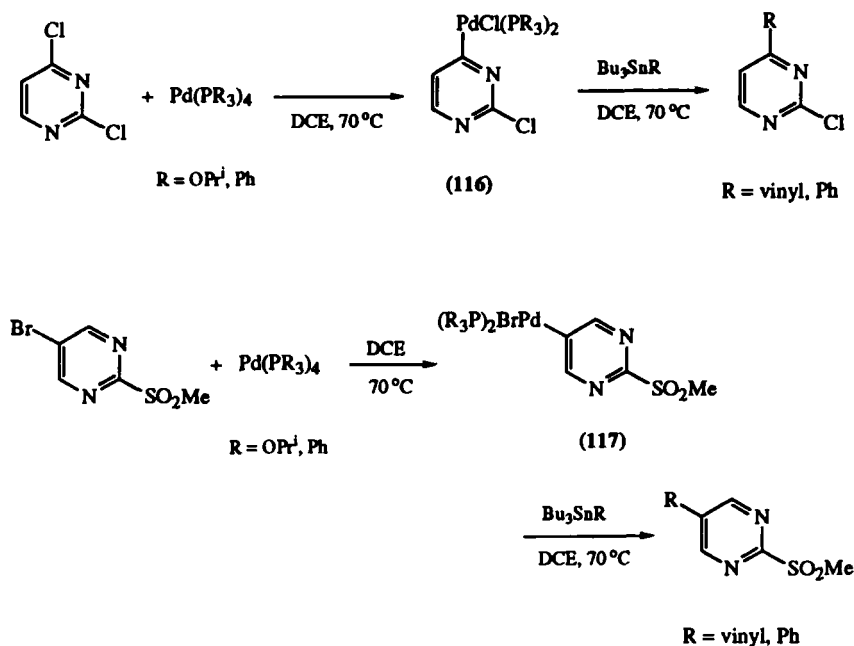
SCHEME 24

tion is in the 4-position (**113**), subsequent phenylation is in the 5-position (**114**), and finally thienylation is in the 2-position (**115**) [89ACSA(B)62].

From reactions between 2,4-dichloropyrimidine or 5-bromo-2-methylsulfonylpyrimidine and tetrakis(triphenylphosphine)- or tetrakis(triisopropylphosphite)palladium the 1 : 1 insertion complexes (**116**) and (**117**) have been isolated (Scheme 25). The regioselectivity of the insertion reaction in 2,4-dichloropyrimidine is in agreement with the 4-regiochemistry in the coupling reactions (see below). The insertion complexes can be purified by conventional methods. The palladized pyrimidines react readily with organostannanes, and may serve as catalysts in coupling reactions between the respective pyrimidine precursor and stannanes (90ACSA927).

The 4-position in pyrimidine is sufficiently activated for displacement of a chlorine by an alkyl group. This has been used for hydroxymethylation (**118**) (Scheme 26) where the hydroxy group of the reagent is protected by a bulky silyl group during the coupling (89T993).

Oxidation of a sulfide to sulfone (**119**) gives a strongly electron-withdrawing group, which promotes coupling in the chloro-substituted 4-position (**119**); a butyl group can be substituted into the 4-position under standard conditions (89ACSA62). The halogen in 2- and 4-chlorodimethylpyrimidines (**120**) can be replaced in reactions run in DMF in the presence of tetraethylammonium chloride and K_2CO_3 . A chlorine in the 5-position is not active; a 5-iodo or 5-bromo substituent is required, but iodine is preferable. In 4,5-dichloropyrimidine (**121**) the substitution is in

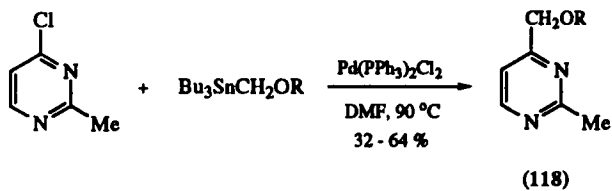


SCHEME 25

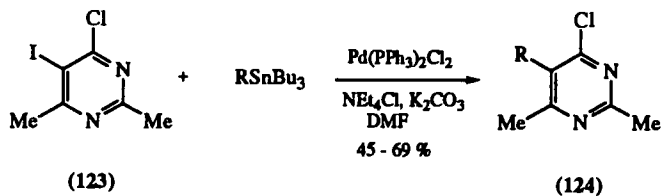
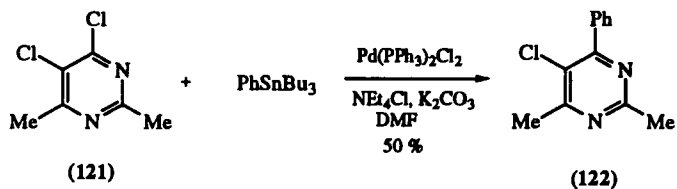
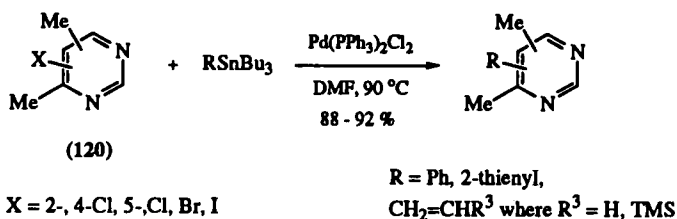
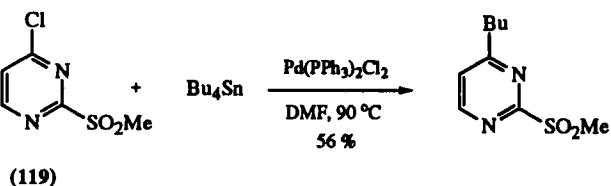
the 4-position (**122**); but in the 4-chloro-5-iodo derivative (**123**), the first coupling reaction is in the 5-position (**124**) with iodine substitution. The 5-bromo-4-chloro analog in reaction with phenyltributylstannane gives 4,5-diphenylation (50%) together with some of the 5-phenylated derivative (7%) (89CPB2814). For comparison, selective coupling in the 4-position is effected using a 4-chloro-5-bromopyrimidine derivative, as discussed above for the preparation of (**113**) [89ACSA(B)62].

Coupling of the *tert*-butyl ether of 5-bromouracil (**125**) with *N*-methylpyrrol-2-yl(trimethyl)stannane gave the expected product (**126**) in low yield (Scheme 27). Modest yields of coupling products (**127**) were also obtained in reactions with 2-thienyl- and 2-selenylstannanes and unprotected iodouracil. With the pyridylstannane only the 3-isomer showed some reactivity. Silylation of 5-bromouracil is recommended before the coupling reaction. Silyl-protected uracil (**128**) reacts with formation of a number of biheteroaryl derivatives (**129**) including pyridylstannanes, except for the 4-isomer (90JHC2165).

α -Stannylated enol ethers provides a general and convenient substrate for the introduction of acyl groups into azines (Scheme 28) [89-

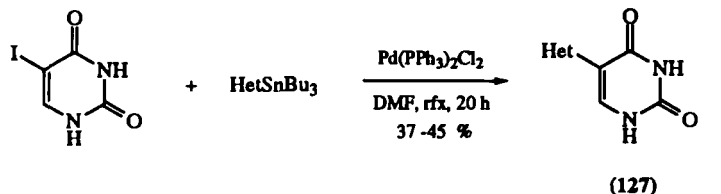
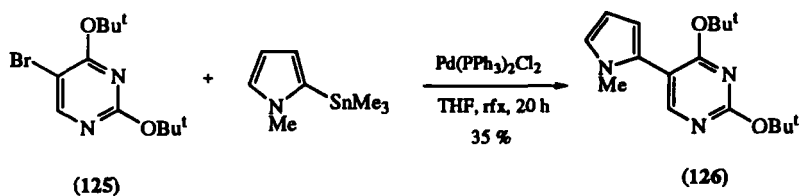


R = Me, SiMe₂Bu^t,
SiMe₂Thx, SiPh₂Bu^t

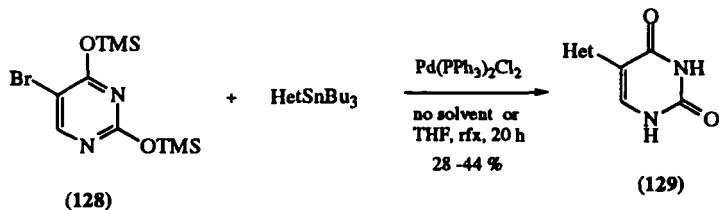


R = 2-thienyl, CH=CHR¹
where R¹ = H, TMS, I

SCHEME 26



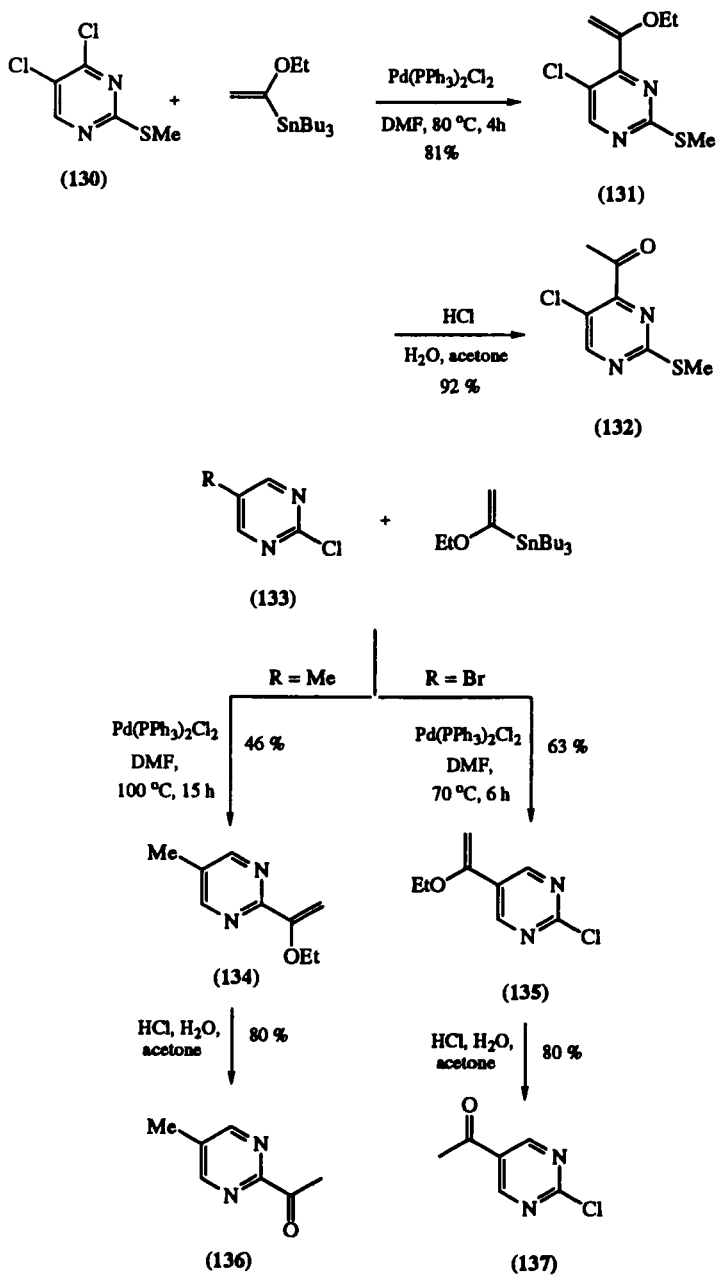
Het = 2-thienyl, 2-selenyl



Het = 2-thienyl, 2-selenyl, 2-thiazolyl,
N-Me-2-pyrrolyl, 2-, 3-pyridyl

SCHEME 27

ACSA(B)62]. The stannanes are available from enol ethers by α -lithiation and quenching with trialkylstannyl chloride. The coupling reactions have been run on derivatives that had either a chlorine atom in an activated position or a bromine atom in the benzenoid position. Mild acid hydrolysis of the α -pyrimidinylalkenyl ethers yields ketones, the acyl-substituted pyrimidines. In the 4,5-dichloro derivative (130), the masked acyl group is introduced into the electrophilic 4-position (131). In the 2,5-disubstituted pyrimidine (133), having a methyl group in the 5-position and a chlorine atom in the 2-position results in the addition of a masked acyl group in the electrophilic 2-position (134). When the 5-substituent in the latter example is a bromine atom, the chemoselectivity leads to masked acylation in 5-position (135). This reaction sequence constitutes a convenient

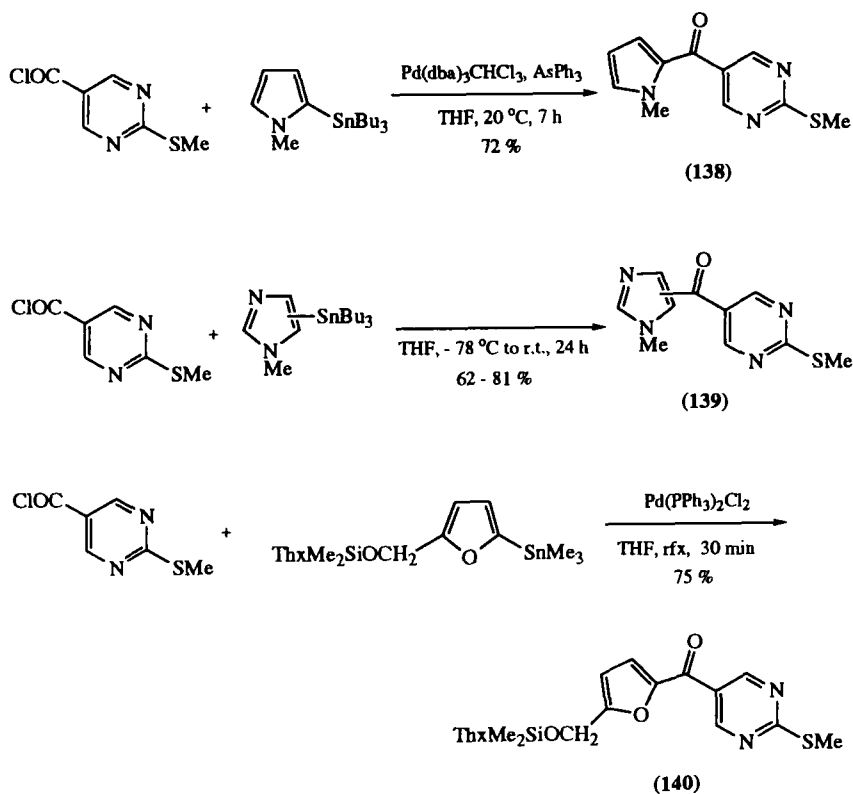


SCHEME 28

method for the introduction of an acyl function into any pyrimidine position (**132**, **136**, **137**), or more generally into most heterocycles [89ACSA(B)62].

In the benzenoid 5-position in pyrimidines, ketones have also been prepared from carbonyl chlorides using the Sn–Pd methodology (Scheme 29). 5-(2-Pyrrolylcarbonyl)pyrimidine (**138**) is available from pyrimidine-5-carbonyl chloride in a Pd-catalyzed reaction with the corresponding 2-pyrrolylstannane. The catalyst was ligated to triphenylarsine, since the complex with triphenylphosphine was not active enough for a satisfactory conversion in this reaction. When the polarization of the reactants is reversed, however, triphenylphosphine is a good ligand for the Pd-catalyst (see below).

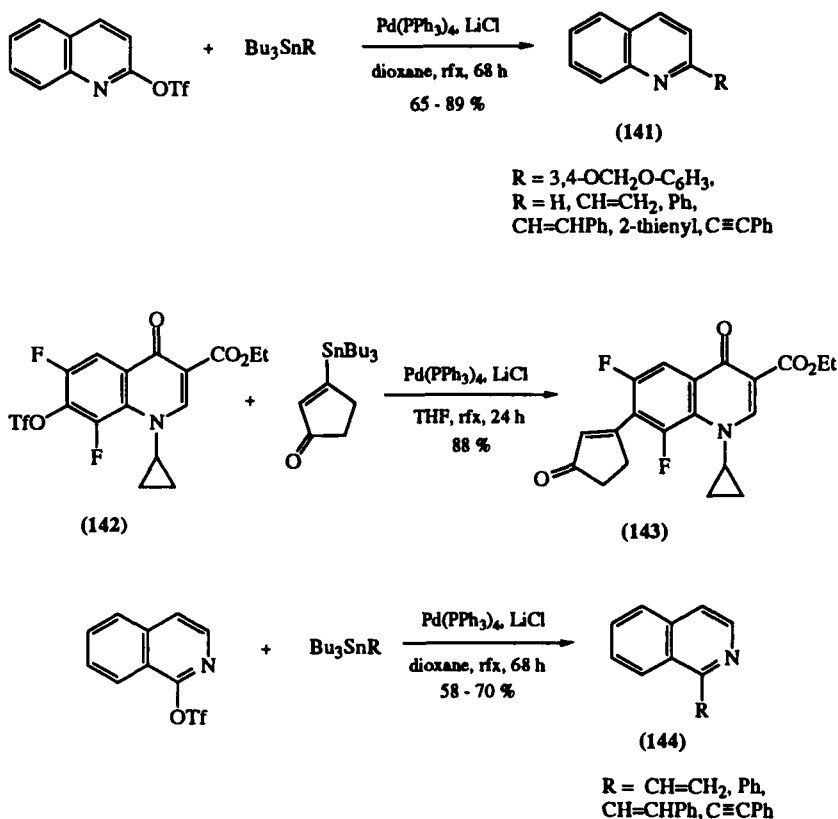
In the preparation of the imidazolyl ketones (**139**), the presence of a Pd-catalyst in the reaction had a deleterious effect. These reactions are



SCHEME 29

best effected without a catalyst. The reaction with 2-stannylimidazole is run at -78°C , and the 5-isomer at room temperature. The stannylated imidazoles are available by metal exchange in 2-lithioimidazole and in 2,5-dilithiated imidazole followed by aqueous destannylation in the 2-position (93ACSA57). Lithiation and metal exchange can also be used to prepare 5-stannylated furfuryl silyl ethers for the synthesis of 5-pyrimidinyl 2-furyl ketones (**140**) using PdCl_2 with triphenylphosphine as ligand. The bulky *tert*-butyldimethylsilyl group (TDMs) is used for hydroxyl-group protection since bulky silyl ethers are not cleaved under the conditions of the coupling reaction (91ACSA914).

The Pd-catalyzed coupling reaction of aryl triflates with alkyl, alkenyl, alkynyl, and aryl tin reagents in the presence of lithium chloride gives high product yields under mild conditions (Scheme 30). In azines the



SCHEME 30

reaction was first reported for 2-quinolyl triflate, which was coupled with 5-(trimethylstannyl)-1,3-benzodioxole to furnish the intermediate (**141**) for the alkaloid dubamine (87JA5478). The triflate is available from the 2-quinolinone and triflic anhydride in pyridine. A number of additional coupling products (**141**) in the 2-position of quinoline have been prepared (89AJC279).

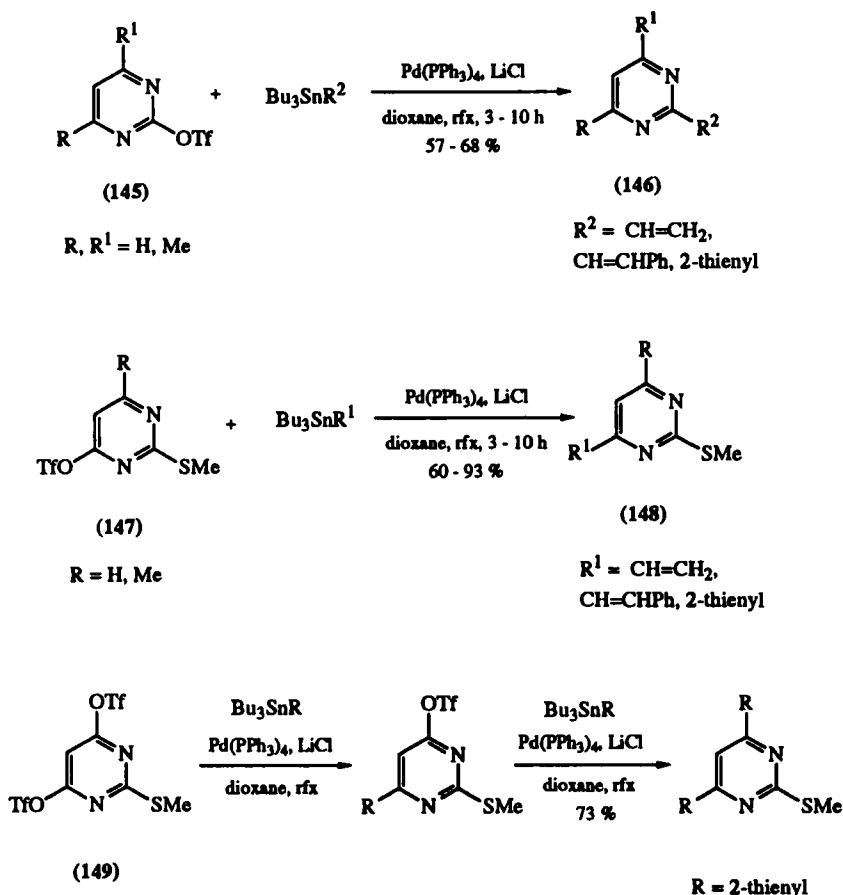
Several examples are known for coupling of triflyloxy derivatives in the carbocyclic part of benzo-fused azines. 8-Quinolyl triflate reacts in the same manner as aryl triflates (87JA5478; 89AJC279). Another example is provided by the 6,8-difluoro-7-triflyloxyquinoline (**142**), which has been used in a coupling reaction with 3-tributylstannylcyclopent-2-enone to form (**143**) (90TL1837).

Triflation of 4-quinolinone has been reported to be difficult, whereas 1-isoquinolinone readily forms a triflate, which is used in coupling with stannanes (89AJC279). The peri-interaction in 1-isoquinolyl triflate interferes in the coupling with bulky stannanes. With tributylphenylstannane the yield of phenylated product **144** was 10% after 24 h at 100°C; the yield was increased to 30% when the reagent was changed to trimethylphenylstannane. The presence of zinc chloride promotes the reaction. The effect of the zinc salt is rationalized as a transfer of the phenyl group to zinc, thereby generating a phenylzinc species which reacts further with the Pd-catalyst. Methylation with tetramethylstannane was not successful (89AJC279). Alkylaluminum reagents may be a better choice for alkylation reactions (see below).

Pyrimidine has been triflated in the 2-position (**145**), the 4-position (**147**), and in both the 4,6-positions (**149**) (Scheme 31). Both 2- and 4-pyrimidinyl triflates were readily coupled with stannanes in the presence of lithium chloride to give **146** and **148** (94H501). The pyrimidinyl triflates show comparable reactivity to chlorides in electrophilic positions. It is recommended that the triflation of pyrimidinones be carried out at low temperature (–78°C). Thereafter, the temperature is raised slowly to room temperature. Triflation carried out in this manner gives products stable enough for purification by preparative chromatography.

Tetraphenylstannane, where the phenyl group may carry various substituents, has been used in the phenylation of chloropyrazines (Scheme 32). Product formation (**151**–**153**, **155**) requires reflux in DMF in the presence of Na₂CO₃. Dechlorination is a problem (**154**) in substrates that are sterically crowded around the halogen (86H785; 89H123). Arylstannanes are available by transmetalation of the corresponding Grignard reagents with tin tetrachloride (89H123). Butylation can be effected in these systems with tetrabutylstannane (89H123).

Tetraphenylstannane reacts in the same manner with 2-chloropyrazine

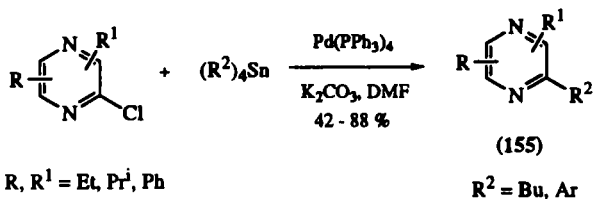
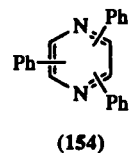
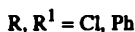
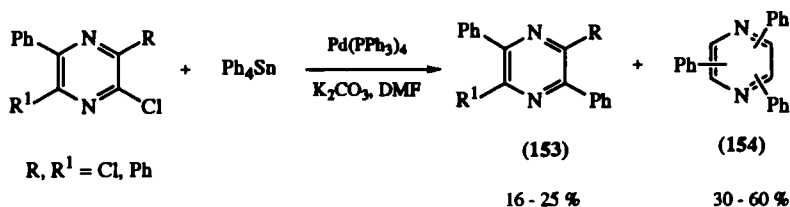
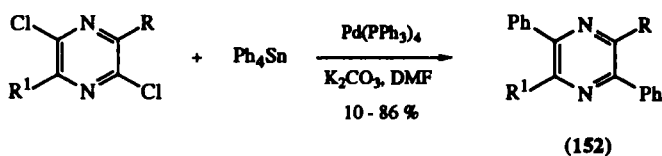
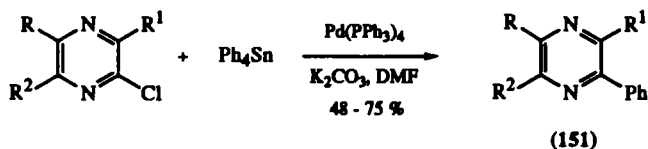


SCHEME 31

1-oxides and 2-chloropyrazine 4-oxides (Scheme 33). Again, dechlorination is a problem (**157**, **159**) in substrates sterically crowded around the halogen. Dechlorination in 2-chloropyrazine 1-oxides was particularly pronounced and can become a major pathway (**157**) (86H785; 89H123).

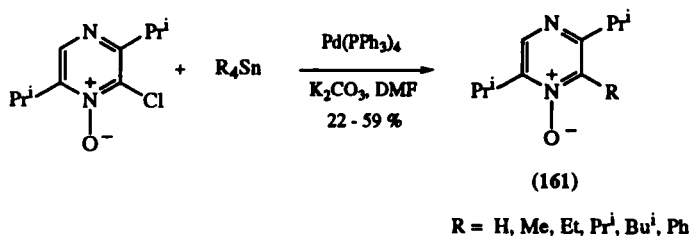
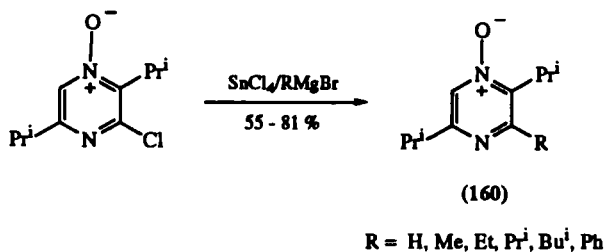
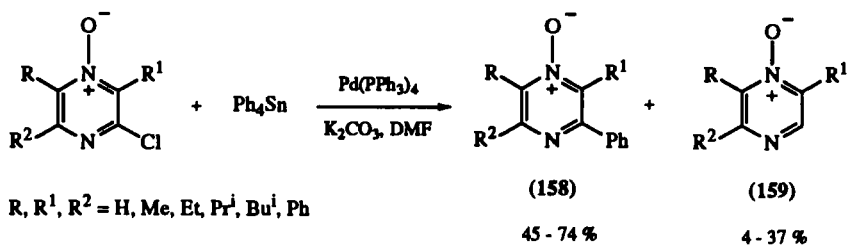
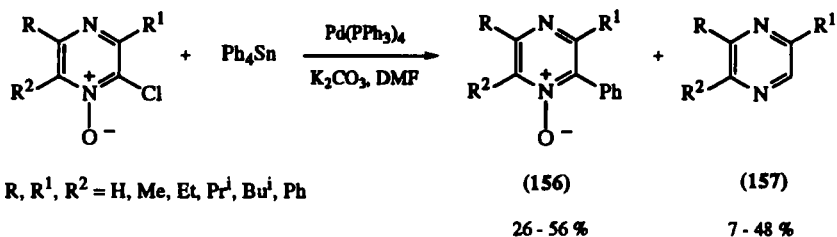
The 7-position in 1,8-naphthyridine is electrophilic; coupling of the 7-chloro-1,8-naphthyridine (**162**) with 1-*tert*-butyloxycarbonylamino-3-tributylstannyl-2-cyclohexene shows the expected readiness for product formation (**163**) (Scheme 34) (90TL1837).

b. *Pyrimidine Nucleosides*. In the 5-position of 2'-deoxyuridine, alkenylation reactions of the 5-iodo derivative with functionalized alkenyl-



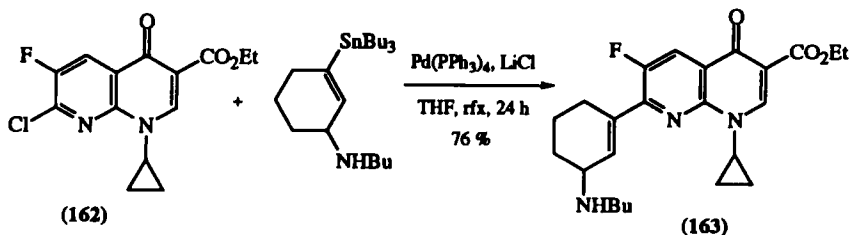
SCHEME 32

stannanes and Pd-catalysis give moderate to good yields of the 5-alkenyl-2'-deoxyuridine (**164**) (Scheme 35) (89SC2117). 5-Triflyloxy analogs react similarly. Thus 5-trifluoromethanesulfonyluridine triacetate undergoes a Pd-catalyzed coupling with alkenyl- and arylstannanes to the corresponding 5-substituted uridines (**165**). Neither electron-donating nor electron-withdrawing groups in the vinyl or phenyl moieties of the stannanes have any significant effect on the course or yield of the reaction (90TL1347).



SCHEME 33

Palladium-catalyzed coupling between halogenated nucleosides and arylstannanes containing a boronic acid substituent (see below) in the aryl group proceeds chemoselectively at the C—Sn bond rather than at the C—B bond to give boron-containing nucleosides (166). The methodology



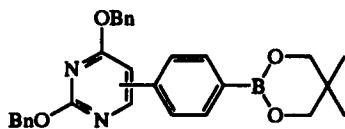
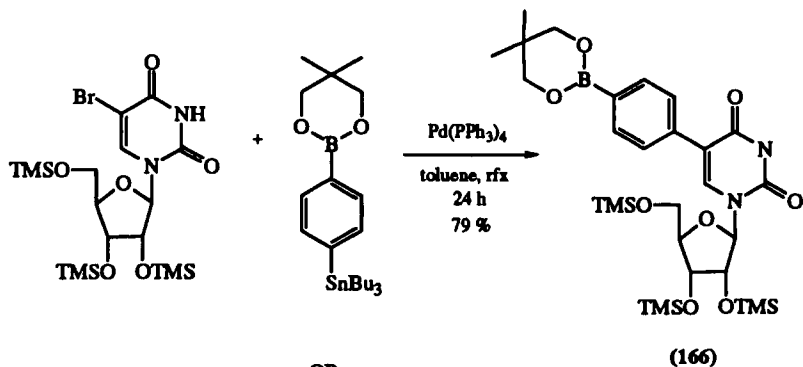
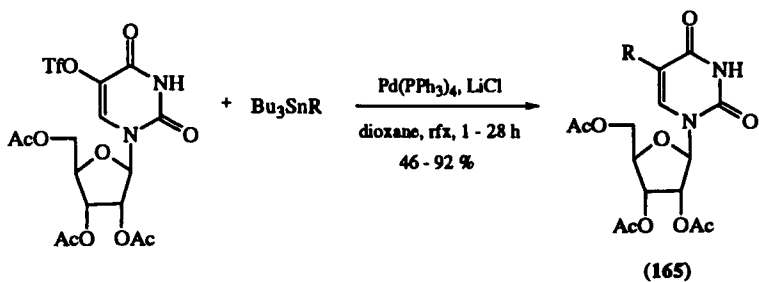
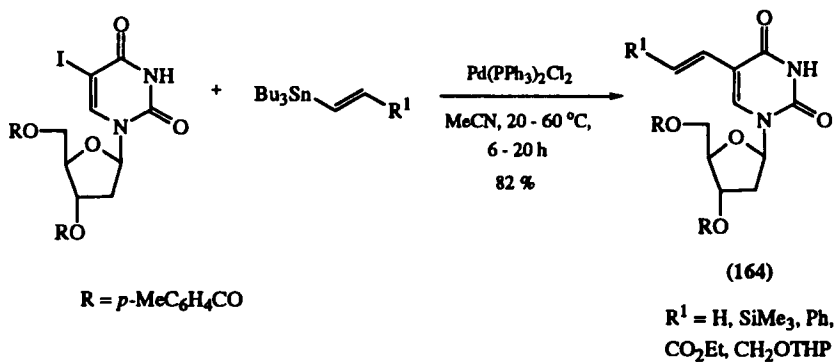
SCHEME 34

was developed to provide ^{10}B -containing nucleosides for neutron-capture therapy (89JOC4734). The chemoselectivity achieved depends on such conditions as a solvent of low polarity (toluene) and the choice of Pd-catalyst—the superior catalyst being $\text{Pd}(\text{PPh}_3)_4$. Bulky silyl-group protection is used for the hydroxyl groups in the sugar moiety. Formation of the chemoselective coupling product (166) from 5-bromouridine under these conditions is shown. The same conditions can be used to introduce the benzenboronic acid moiety into the 5-position (167) of *O*-benzyl protected 5-iodouracil, and into the 6-position (168) in *O*-benzyl-protected 6-bromouracil (89JOC4734).

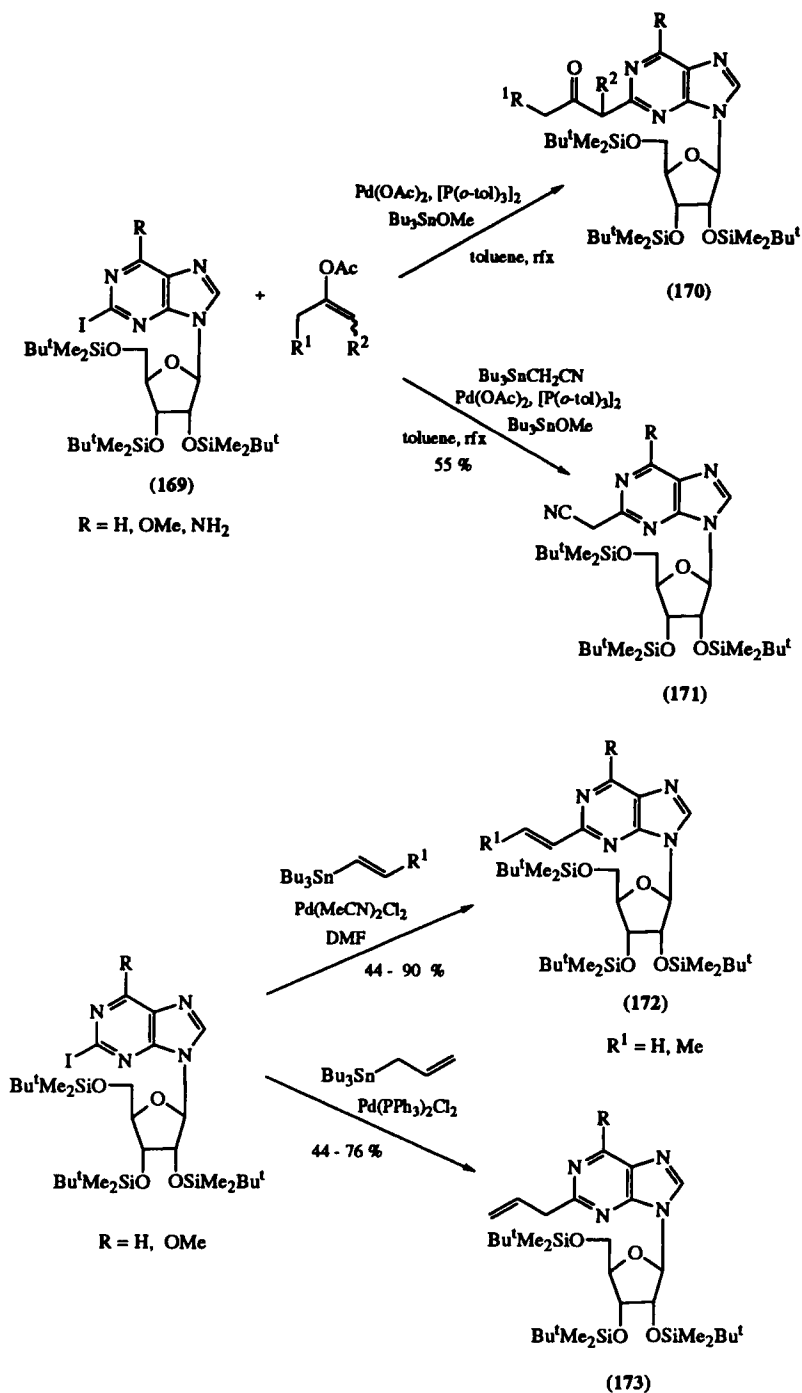
c. Purine Nucleosides. Palladium-catalyzed cross-coupling reactions of 2-iodopurines (e.g., 169) with organostannanes offer a highly efficient approach for synthesis of new 2-functionalized purine nucleosides (Scheme 36). Palladium-mediated ketonylation with tributylstannyl enolates gives the ketones (170). Prior to the coupling, the ketones are converted to enol acetates, which react with tributylstannyl methoxide to form the tributylstannyl enolate in situ for the coupling (87JA7223; 88JOC3051; 88S848).

Extension of the cross-coupling reaction to include other functionalized organostannanes includes tributyl(cyanomethyl)stannane for transfer of the cyanomethyl group to the 2-position in *O*⁶-methylinosine (171), which is silyl-protected in the ribosyl moiety (88JOC3051).

Alkenylation occurs in the 2-position in a 2-iodo purine nucleoside and a tributylalkenylstannane; with vinylstannanes, the 2-alkenylpurines (172) are obtained (87JA7223; 88S848). Further applications include preparation of the unsaturated nucleosides 2-allylinosine [2-(2-propenyl)inosine] (173) and 2-alkenylinosine (172). In the temperature range 90–95°C the expected 2-allylinosine (173) is obtained. But at slightly higher temperature, at 105°C, the *trans*-methylethenyl derivative (172) is obtained because isomerization during the reaction results in migration of the double bond into conjugation with the heterocycle (89T3653).



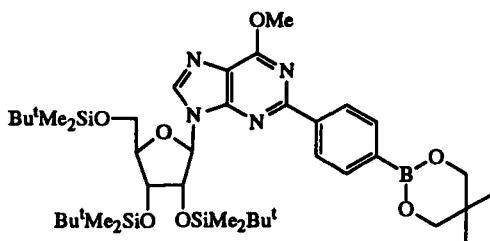
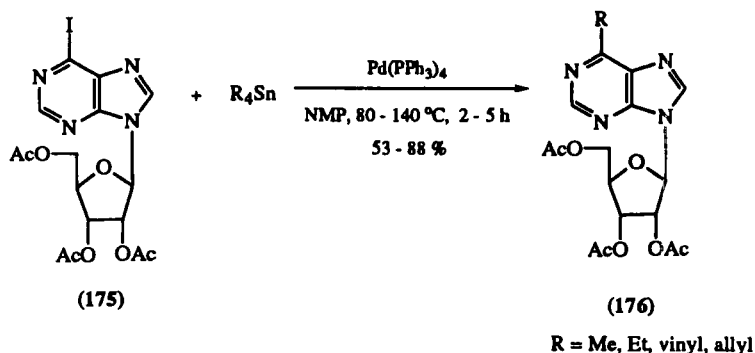
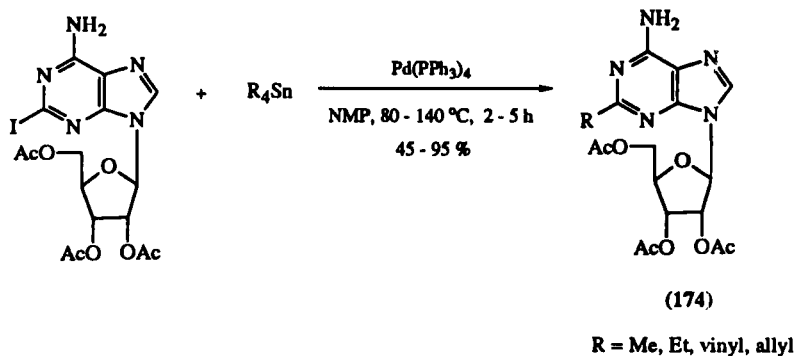
SCHEME 35



SCHEME 36

In alkenylation of *O*-methylinosine, protection of the carbohydrate moiety is not necessary; the coupled nucleoside is obtained in almost quantitative yield (88JOC3051).

Purine nucleosides have also been alkylated in the 2-position using tetraalkylstannane reagents (Scheme 37). Methyl- and ethyl-substituted



SCHEME 37

analogs have been prepared. *N*-Methylpyrrolidinone (NMP) is recommended as the solvent in the reaction with tetraalkylstannanes. The reactions with the methyl- and ethenyltin reagents were run at 80°C, the allyltin at 110°C and the ethyltin at 140°C, reflecting the relative coupling reactivities of these reagents in the formation of the 2-alkylated nucleoside (**174**). On alkylation in the 6-position of the purine (**175**), isomerization of the allyl moiety to its ethenyl isomer could not be avoided. Methylation and alkenylation in the 6-position (**176**) are effected by tetramethyl- and tetraethenylstannane (93JMC2938).

Adenosine and its 2'-deoxy and 2',4'-dideoxy analogs can be persilylated and coupled in the same manner in the 8-position to furnish 8-alkylated or alkenylated products in 65–92% yields (93JMC2938).

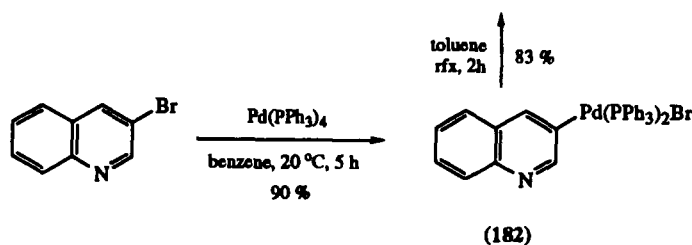
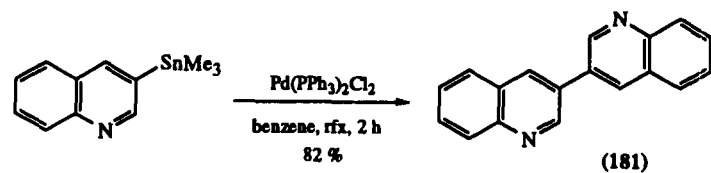
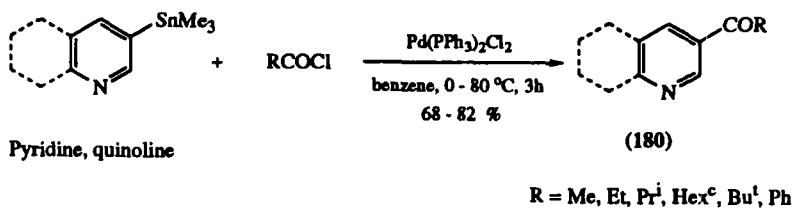
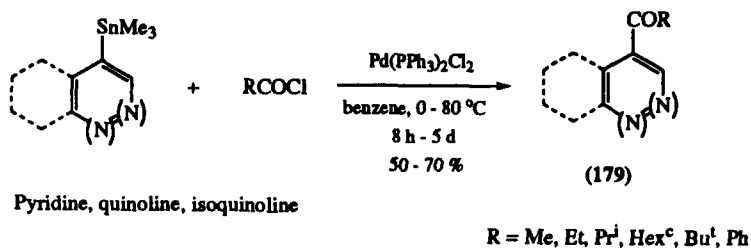
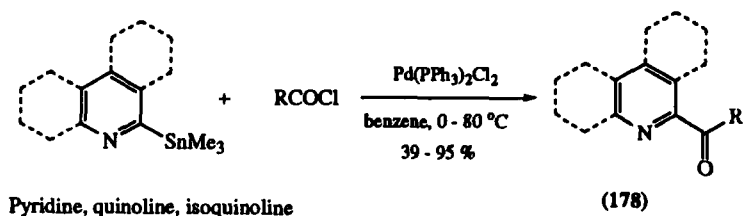
As in the pyrimidine nucleosides discussed above, Pd-catalyzed coupling between a 2-iodo purine nucleoside and arylstannanes containing a boronic acid substituent in the aryl group proceeds chemoselectively at the C—Sn bond rather than at the C—B bond to give boron-containing nucleosides (**177**) (89JOC4734).

3. Stannylation and Reactions of Stannylazines

a. *Pyridine, Quinoline, and Isoquinoline.* Pyridine, quinoline, and isoquinoline have been stannylated in the 2- (1-position in isoquinoline), 3-, or 4- position (82CPB1731) (Scheme 38). In reactions with acid chlorides the 2-trimethylstannylazines and their 1-isoquinoline analogs are transformed into corresponding ketones (**178**), most of them at room temperature without a catalyst. However, in the 4-position, which is electronically similar to the 2-position, ketone formation (**179**) requires the promoting effect of a Pd-catalyst.

Reactions of 3-trimethylstannyl derivatives to form the coupling products **180** also require a catalyst. In the 4-position the yields are moderate to good, apart from a ketonylation reaction of quinoline which gave low yields with aliphatic acid chlorides. In the 3-position the yields are good. For 3-stannylazines the desired cross-coupling is frequently accompanied by considerable homo-coupling, i.e., dimerization of the heterocycle to 3,3'-bipyridine, -isoquinoline, and -quinoline, (**181**) and their 4,4'-isomers (82CPB2003). When desired, homo-coupling of 3-stannylquinoline is achieved under the above conditions in the absence of an acid chloride.

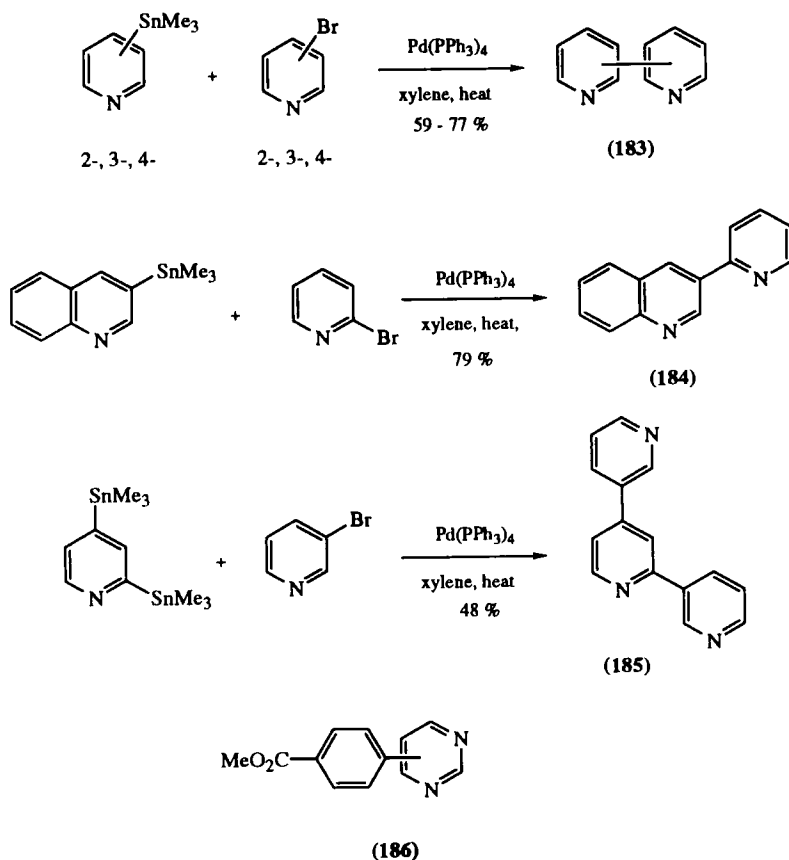
The intermediate organopalladium (**182**) complex in the coupling reactions has been isolated from reactions between equimolar amounts of 3-bromoquinoline and the Pd(0)-catalyst. The complex can be cross-coupled with the corresponding stannyl derivative to the apparent homo-coupled product **181** (82CPB2003).



SCHEME 38

Bipyridine formation has been further explored in a series of reactions between stannylated pyridine and bromopyridines or benzo-fused homologs (Scheme 39), and has yielded a series of regioisomeric bipyridines (**183**). 3-Trimethylstannylquinoline reacts readily with 2-bromopyridine to furnish **184**. 2,4-Distannylated pyridine can be coupled twice with 3-bromopyridine to form **185** (86S564). Coupling with 4-iodobenzoic acid ester proceeds equally well (**186**) (86TL4407).

b. *Pyrimidines*. Stannylpyrimidines are generally good substrates for Pd-catalyzed reactions with organohalides and triflates. Some information on their preparation is therefore given. Generally, stannylation is effected by a transmetallation reaction between an organostannyl chloride and a



SCHEME 39

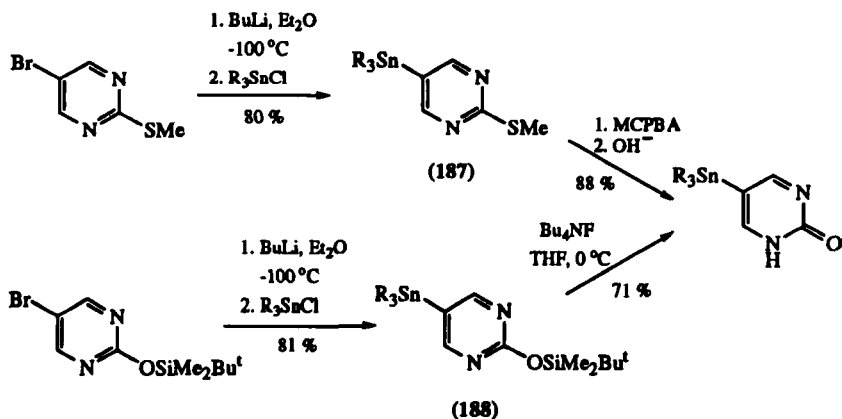
lithiated species. This method works well in the benzenoid position in pyrimidines (**187**, **188**) (Scheme 40). The lithiation is run at low temperature in order to avoid adduct formation between the lithium reagent and an activated position in pyrimidine, and the metal-metal exchange is effected by quenching the lithiated species with a trialkylstannyl chloride [88-ACSA(B)455; 89JCS(P1)255].

Stannylation in the electrophilic 4-position can be effected by thermal decarboxylation of the corresponding carboxylate (**189**, **190**) (Scheme 41). The reaction is promoted by Pd-catalysis (89T993). Stannylation can also be effected on the 4-iodopyrimidine (**191**) using hexaalkyldistannanes in the presence of fluoride ions and $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ (89T993). Bis(π -allyl)palladium chloride is the recommended catalyst for the coupling of 5-bromopyrimidines (**193**) with hexaalkyldistannanes to the stannanes (**194**). The presence of halide ions promotes the reaction, especially fluoride ions [89ACSA(B)684]. The promoting effect is ascribed to the high affinity of fluoride ions for tin.

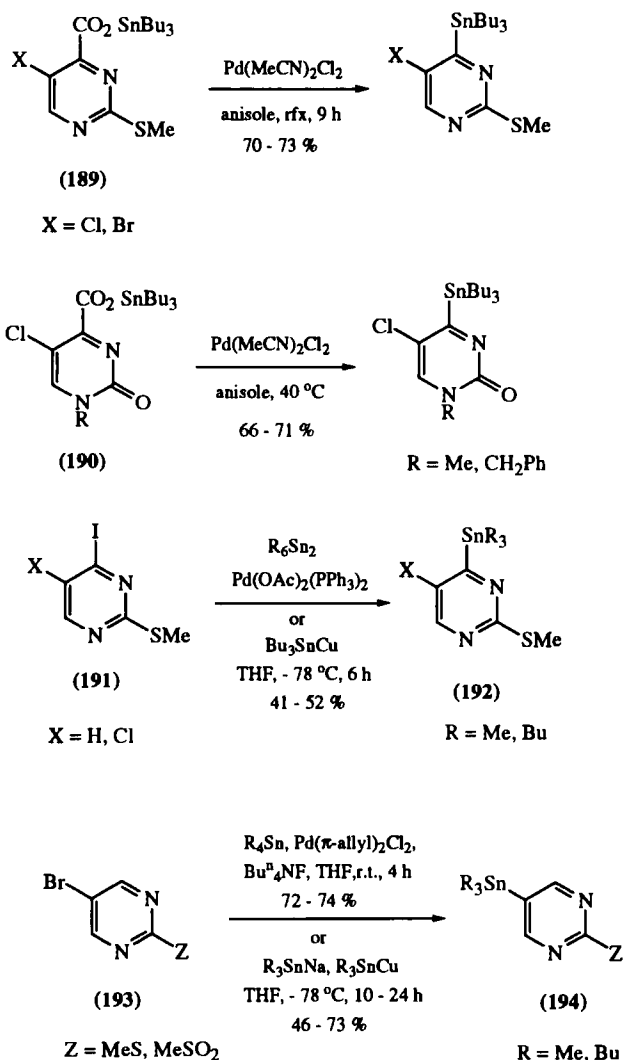
A halogen atom in an electrophilic position can be substituted using a metal stannate. Reactions of the 4-iodo derivative (**191**) with stannyl lithium, -sodium, or -copper reagents are run at -78°C to form the 4-stannane (**192**) (89T993).

5-Bromo-2-chloropyrimidine is stannylated in the 5-position (**195**) (Scheme 42). The reaction of 2,4-dibromopyrimidine with trimethylstannylsodium results in regioselective substitution in the 2-position to furnish 4-bromo-2-trimethylstannylpyrimidine (**196**), whereas reactions with the corresponding stannyl lithium reagent failed (94T275).

The regiochemistry is not in accord with the relative reactivity



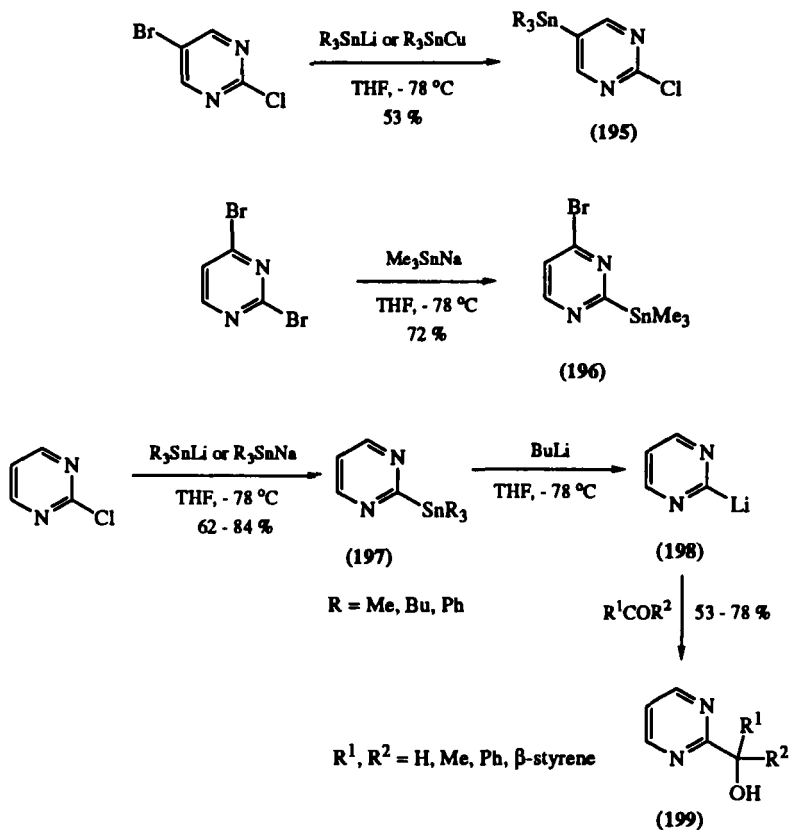
SCHEME 40



SCHEME 41

of pyrimidines toward nucleophiles (94T275). In the 2-position, 2-chloropyrimidine is stannylated (197) by tributyl-, trimethyl-, or triphenylstannyllithium (94T275).

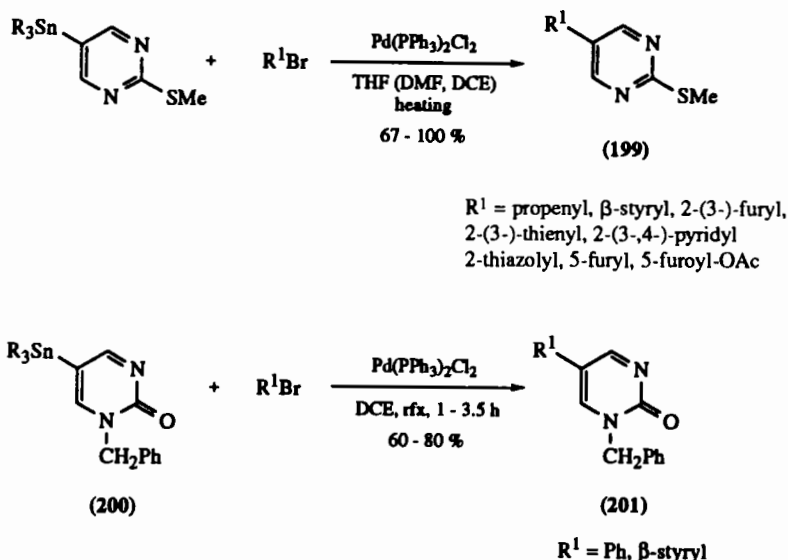
Direct stannylation in the 4-position has not been successful. 4-Iodo-2-methylthiopyrimidine has been stannylated by way of lithiation, followed by quenching with a stannyl chloride. However, attempts to lithiate 2-



SCHEME 42

chloro-, 2-bromo-, or 2-iodopyrimidine met with little success; adduct formation by the addition of lithiated species to electrophilic pyrimidine positions is a major side reaction. 2-Lithiopyrimidine (198), however, is formed selectively by reversing the order of metal exchange: i.e., a 2-stannylpyrimidine reacts with butyllithium, giving metal-metal exchange to form 2-lithiopyrimidine; the transfer is confirmed by aldol reactions (199) with carbonyl compounds (94T275).

Stannylpyrimidines react readily with organohalides and -triflates under the influence of Pd-catalysis (Scheme 43). The products are the same as those obtained when the substrates are oppositely polarized (see above). 2-Methylthio-5-trimethylstannylpyrimidine reacts with bromostyrene or propenyl bromide to yield 199. 5-Pyrimidinyl biheteroarenes are accessible from bromofurans, bromothiophenes, or bromopyridines as well as stan-



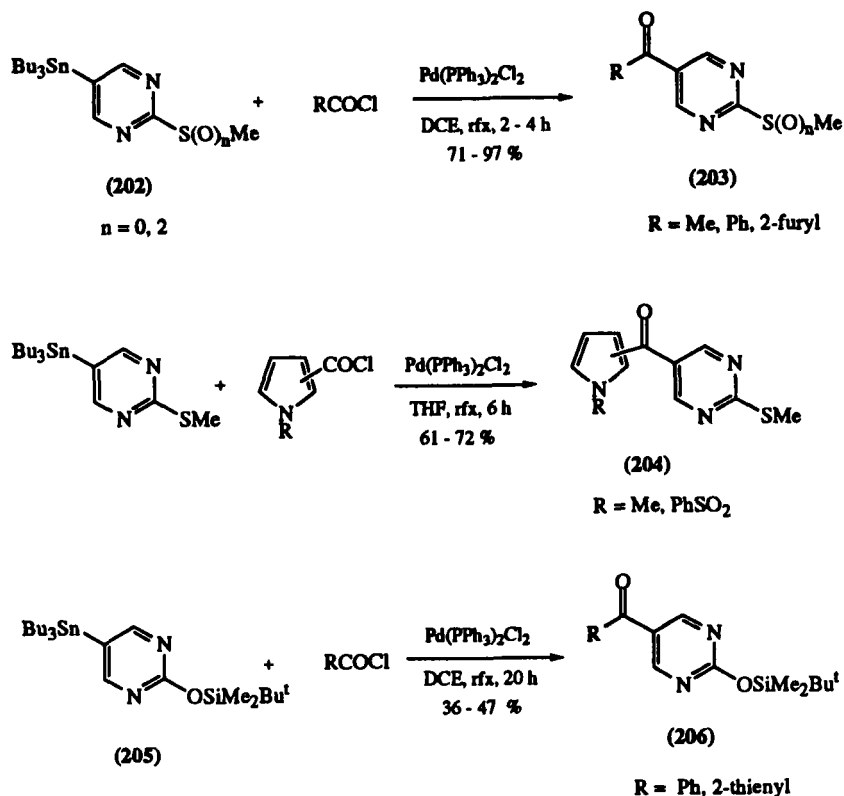
SCHEME 43

nylated pyrimidine. 5-Stannylated 2-pyrimidinones (**200**) are good substrates for coupling reactions (**201**). 4-Stannylpyrimidines react similarly.

Alkyl, aryl, and heteroaryl ketones (**203**) are available from 5-stannylpyrimidines (**202**) and carbonyl chlorides (Scheme 44). The reaction with pyrrole was run on *N*-alkylated or *N*-acylated pyrrolecarbonyl chloride to form the ketones (**204**) (93ACSA57). 2-Pyrimidinones are protected and solubilized as a *tert*-butyldimethylsilyl ether (**205**) for coupling. During the reaction the silyl group is cleaved off. The silyl function, after acylation in the para position (**206**), is sensitive to cleavage because of the electron-withdrawing properties of the acyl group [89JCS(P1)255].

Pyrimidines stannylated in the 4-position are active in coupling reactions. 5-Chloro-4-stannylpyrimidines, either as 2-sulfide or 2-one, are coupled with alkenyl or aryl halides to form **208**, **210**, and **212**. With an acid chloride, ketone **213** is formed in the absence of catalyst, which has an otherwise deleterious effect on the reaction. The reaction between thiophene-2-carbonyl chloride and the 4-stannylpyrimidine is run at -78°C (94T275).

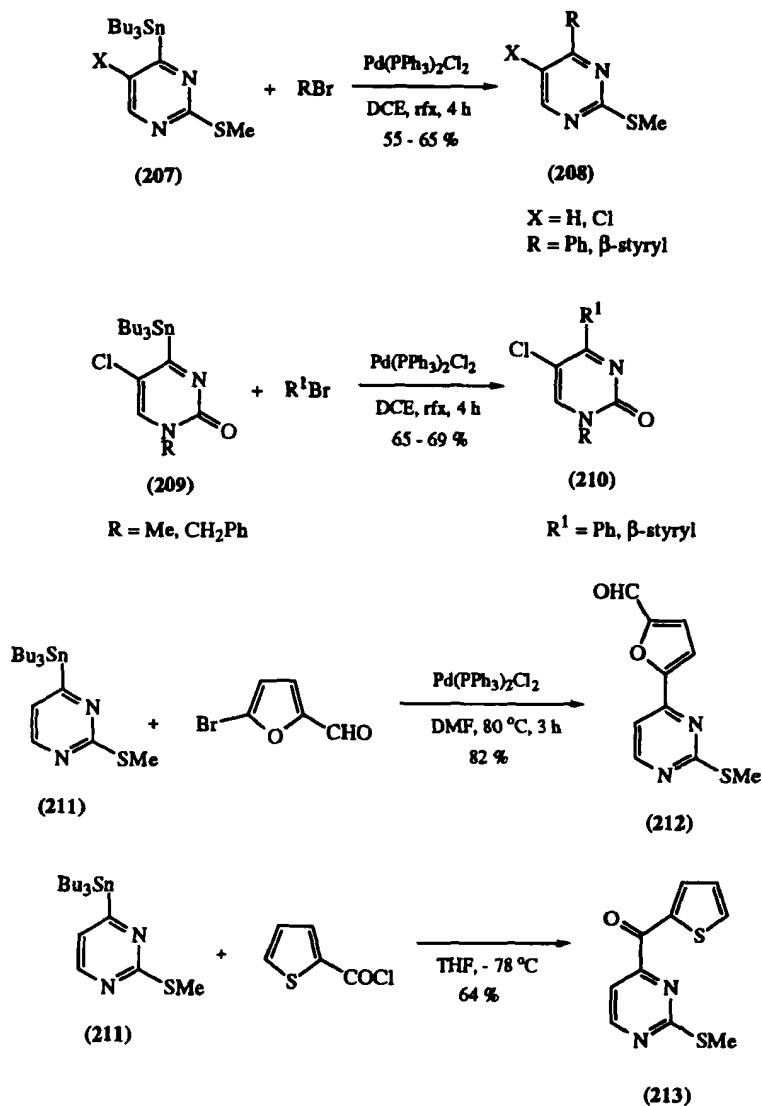
2-Stannylpyrimidines also react with acid chlorides to form ketones (**214**) without a catalyst (Scheme 46). The reaction with furoyl chloride is almost instantaneous at -78°C ; the yield of ketone is 52%. 2-Thienylcarbonyl chloride provides the ketone in 62% yield. On the other



SCHEME 44

hand, in coupling reactions with iodobenzene or β -bromostyrene Pd-catalysis is required for product formation (**215**) (94T275).

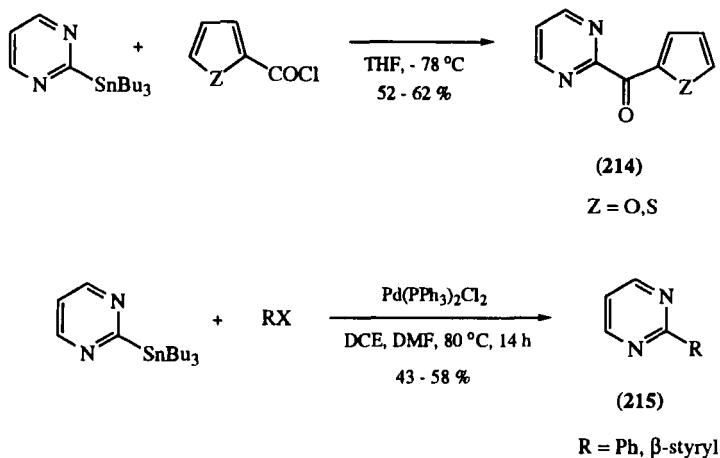
c. *Pyrimidine Nucleosides.* In work on base modification of pyrimidine nucleosides, Sn-Pd transmetalation-coupling has been found to be an efficient entry into 6-derivatized uridines (**218**) (Scheme 47) (93T2533). Lithium diisopropylamide (LDA) in THF at -78°C has been used for regioselective metallation at C6 in **216**, and the stannyl product (**217**) was isolated after quenching with tributylstannyl chloride. Coupling reactions with iodobenzene using various Pd-complexes and solvents were not satisfactory until CuI was added. The protocol for optimal conditions in most cases uses 10 mol% $\text{Pd(PPh}_3)_4$ and 20 mol% CuI in a weakly coordinating solvent (DMF at 80°C). Various substituted ethenyl derivatives can be introduced into the 6-position starting from the corresponding bromides. 1-Iodoalkynyl reagents were used to prepare 6-alkynyluridines. Allylic bromides and propargyl bromide are also suitable as partners in the cross-



SCHEME 45

coupling. Addition of CuI as co-catalyst results in a 25-fold rate enhancement.

The allylic halide function in protected cephem chloride, which has several sensitive functions, could be coupled with **217** in 85% yield to form **219**, thereby high-lighting the mildness of the coupling reaction (93T2533).



SCHEME 46

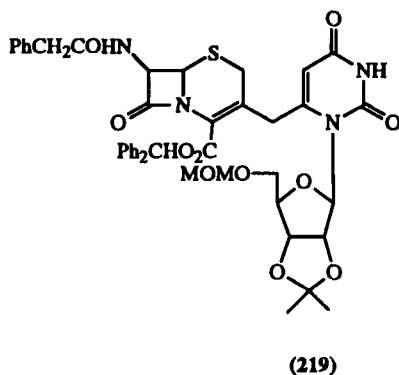
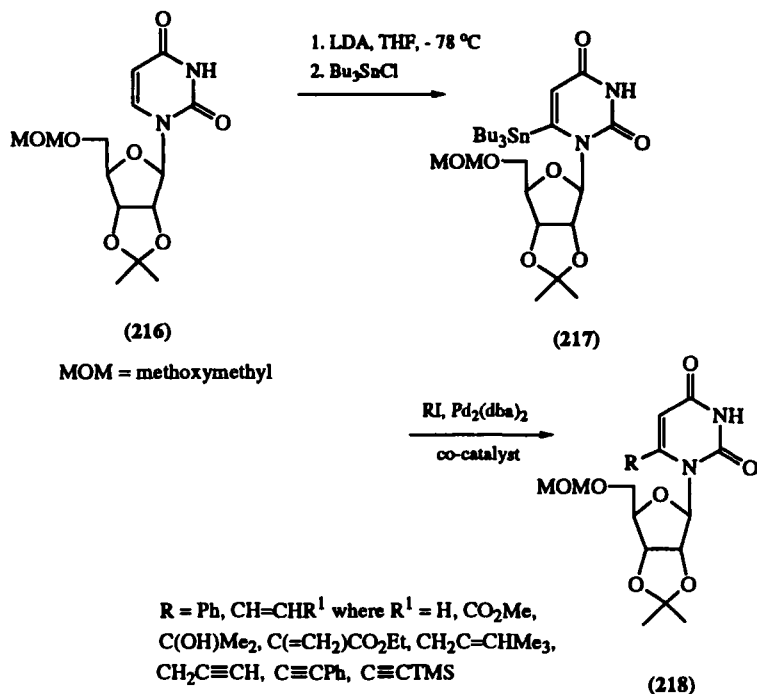
B. ORGANOBORON COMPOUNDS

1. General

Cross-coupling reactions between alkenylboranes and organic halides are effectively catalyzed by Pd(0) in the presence of an aqueous base; phenylboronic acids react in the same way with haloarenes (81SC513). With thallium(I) hydroxide or carbonate these reactions, including reactions with alkylboronic esters, can be carried out under nonaqueous conditions (89CL1405). The organoborane reagents are in general available by metal-metal exchange reactions. Stereo-defined 1-alkenylboranes are available by monohydroboration of alkynes (85JA972).

2. Halogenoazines

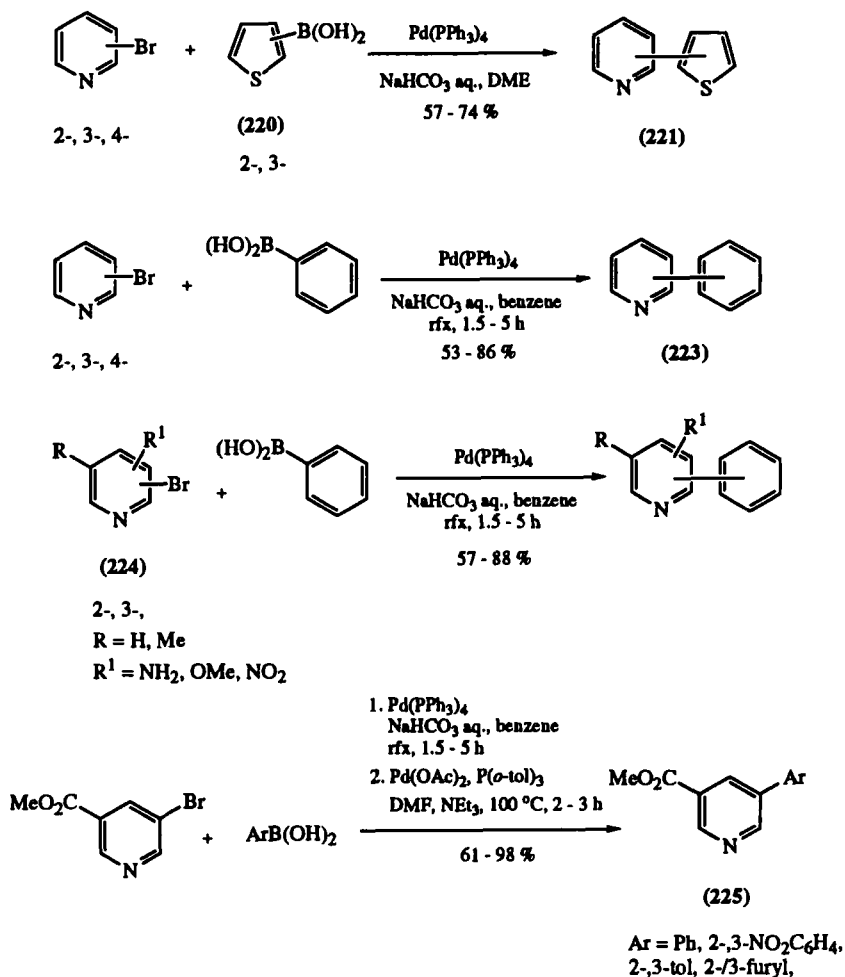
a. *Pyridine*. 2-, 3-, or 4-Bromopyridine can be thienylated using $\text{Pd}(\text{PPh}_3)_4$ as catalyst under basic conditions in reactions with 2- or 3-thiopheneboronic acid (**220**) (Scheme 48). All six isomeric thienopyridines (**221**) have been formed (84CS5). The yields of phenylpyridines (**223**) are of the same order as those in reactions between isomeric bromopyridines and phenylboronic acid. In the benzenoid 3-position bromo- and iodopyridine give the same high yield of coupling products, whereas 3-chloropyridine, like chlorobenzene, failed to react (87H2711). Hydroxy, amino, nitro, or methoxy substituents in the pyridine (**224**) have no signifi-



SCHEME 47

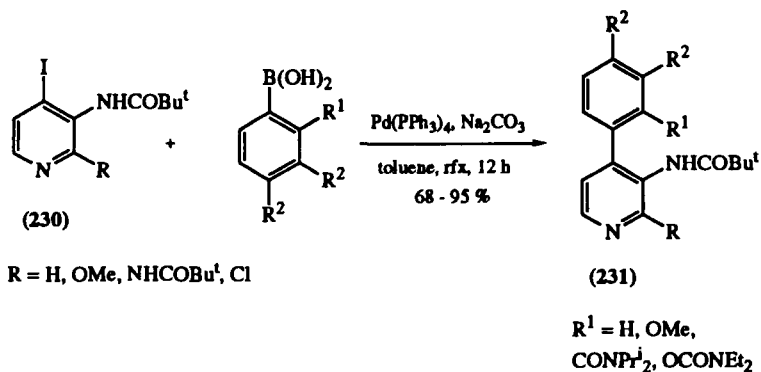
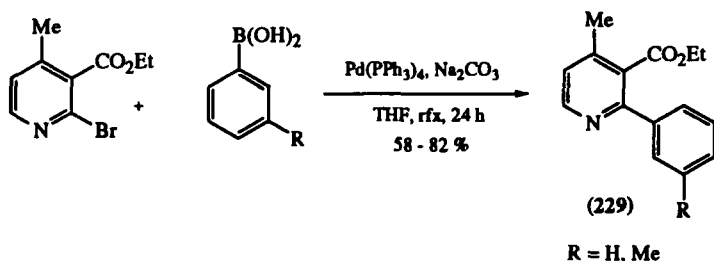
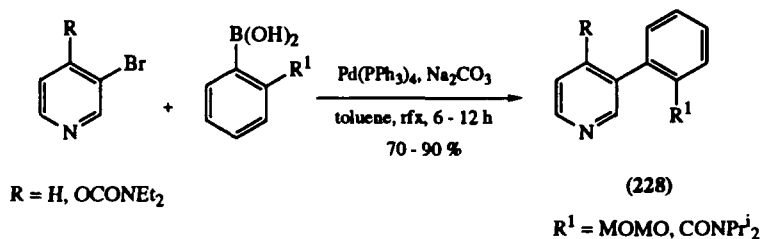
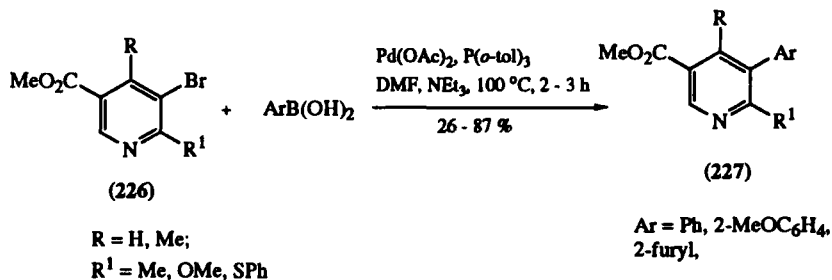
cant effect on the reaction, an exception being 5-bromo-3-hydroxypyridine which failed to react (87H2711). 5-Bromonicotinic acid methyl ester is arylated (**225**) by phenylboronic acid.

6-Methoxy- and 6-phenylthio-5-bromonicotinates (**226**) react with a variety of aryl and heteroaryl boronic acids in coupling reactions (**227**) (Scheme

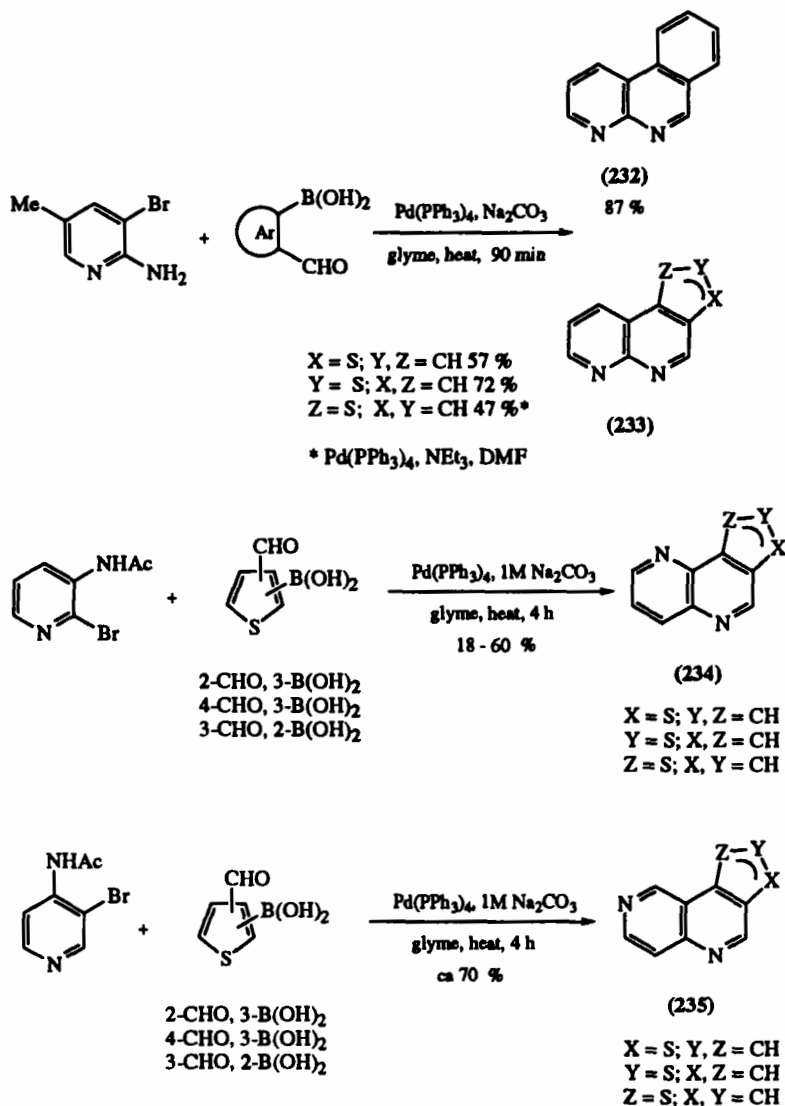


SCHEME 48

49). 4,6-Dimethyl-5-bromonicotinate afforded an 87% yield of 4,6-dimethyl-5-phenylnicotinate with phenylboronic acid. The boronic acid is more sensitive to steric interaction than the bromide in the coupling; 2,4,6-trimethylphenylboronic acid failed to react with 5-bromonicotinate (84JOC5237). The reaction proceeds, however, with 2-substituted phenylboronic acids as in the synthesis of **228** (85TL5997; 87TL5093). Additional substituents in the 3- and 4-positions in phenylboronic acid do not interfere in the coupling with 3-acylamino-4-iodopyridines (**230**) in the preparation of arylated aminopyridines (**231**) [90JCS(P1)2611].



SCHEME 49



SCHEME 50

The reaction between *o*-bromoaniline and 2-formylbenzeneboronic acid by the coupling procedure provides a new method for the preparation of phenanthridine. Applied to 2-amino-3-bromopyridines aza analogs are formed, as exemplified by the benzo[*c*][1,8]naphthyridine (**232**). Isomeric *o*-formylthiopheneboronic acids yield the corresponding thienylpyridines,

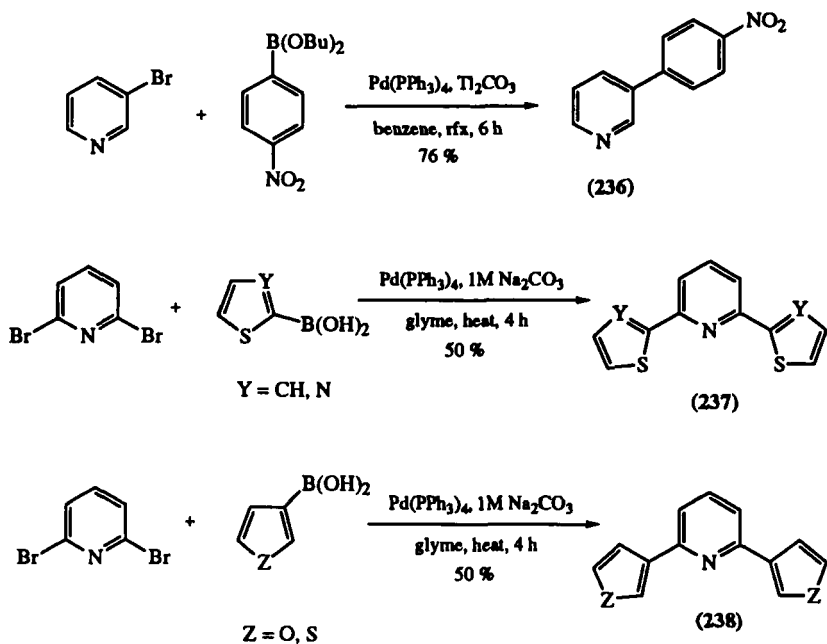
which are subsequently cyclized to thenonaphthyridines (**233**). 3-Formylthiophene-2-boronic acid in the coupling reactions is sensitive to hydrolytic cleavage of the C—B bond. The hydrolysis can be suppressed by working with triethylamine as a base in dry DMF (86CS311).

Two additional series of thieno[*c*]naphthyridines (**234**, **235**) have been prepared from 3- and 4-aminopyridines by essentially the same reaction. Free amino groups in the pyridine are preferably acylated. The change of chlorine to bromine in the 2-position in a 3-aminopyridine had a marked promoting effect on the rate of the reaction. It appears that 2-thienylstannanes are superior reagents for the preparation of thieno[3,2-*c*][1,5]- or -[1,6]naphthyridines (**234**, **235**) in coupling reactions with the bromopyridine amines (91CCC2340). The promoting effect of thallium(I) salts on Pd-catalyzed reactions of boronic acids (87JA4759) was not observed in the heterocyclic coupling reactions discussed above.

Alkyl boronate esters are useful reagents with [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride [PdCl₂(dppf)] or Pd(PPh₃)₄ catalysts, as illustrated for the coupling with the butyl ester of 4-nitrophenylboronic acid to give the substituted pyridine (**236**) (Scheme 51) (89CL1405). Dihalopyridines can be dicoupled. 2,6-Dibromopyridine and 2-thiophene- or 2-thiazoleboronic acid furnished the 2,6-bis(2-thienyl)pyrimidine (**237**). Coupling products (**238**) from 3-thiophene- or 3-furanboronic acids are prepared similarly. In these reactions 20% excess boronic acid is used because of the ease of deboronation, even under weakly alkaline conditions, especially for the π -excessive heterocycles (90H645).

b. *Pyrimidines*. Coupling reactions in simple pyrimidines are illustrated by the reaction between 2-chloropyrimidine and 2- or 3-thiophene- and 2- or 3-selenopheneboronic acids, which give the corresponding 2-substituted pyrimidines (**239**) (Scheme 52). In 2,4-dichloro- or 2,4-dibromopyrimidine, the 4-halogeno substituent is the more reactive, 2-chloro- or 2-bromo-4-(2-thienyl)pyrimidine (**240**) being the product from thiophene-2-boronic acid. It was necessary to protect 5-bromo- or 5-iodouracil before coupling; *tert*-butyl and benzyl derivatives of the uracils were used in the preparation of the biheteroaryls (**241**) (86CS305; 90JHC2165).

c. *Pyrazine*. Pd(dppf)Cl₂ is an efficient catalyst for the reaction between arene- or heteroareneboronic acids and 2-amino-6-halopyrazinecarboxylic acid esters (**242**) in the preparation of **243** (Scheme 53). Thus the 6-bromopyrazinecarboxylic acid is coupled to benzene in 60% yield with the catalyst Pd(PPh₃)₄, and in 82% yield with Pd(dppf)(OAc)₂. It is sug-

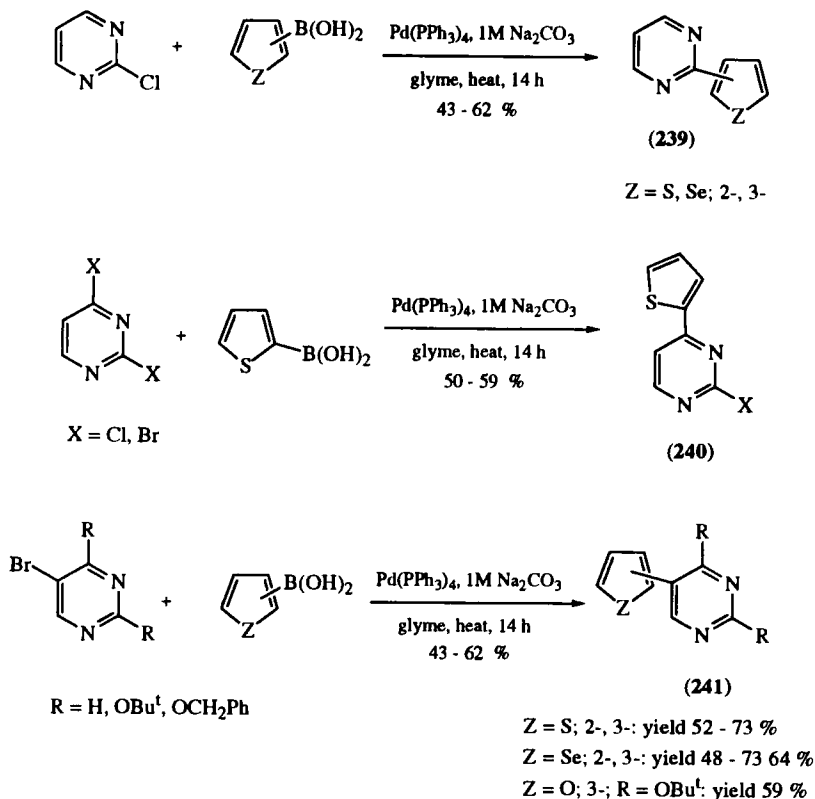


SCHEME 51

gested that the greater efficiency of the binuclear catalyst is caused by decreased steric hindrance enforced by the rigid ferrocene backbone, which acts to "stretch" the Pd—P bond distance from its usual length (88JOC2052). 6-Chloropyrazines also undergo the coupling (**244**, **245**) in reactions promoted by $\text{Pd}(\text{PPh}_3)_4$, but at a slower rate of conversion than that for bromides (89H939).

Alkylation and arylation of 2-chloropyrazines can be carried out as a "one-pot" reaction, where the boron compounds are generated from the corresponding Grignard reagents by boron trifluoride. $\text{Pd}(\text{PPh}_3)_4$ is the catalyst used. The yields are generally in the range 40–50%. Corresponding reactions with organotin compounds appear to give higher product yields (89H939).

d. *Pyrimidine Nucleosides*. Silyl-protected 5-iodouridine or 5-iodo-2'-deoxyuridine (**246**) reacts with arylboronic acids in the presence of a Pd-catalyst to give moderate yields of the corresponding 5-aryluridines and 5-aryl-2'-deoxyuridines (**247**) (Scheme 54). The coupling of arylboronic acids bearing electronegative groups was not successful (e.g., 4- CF_3).

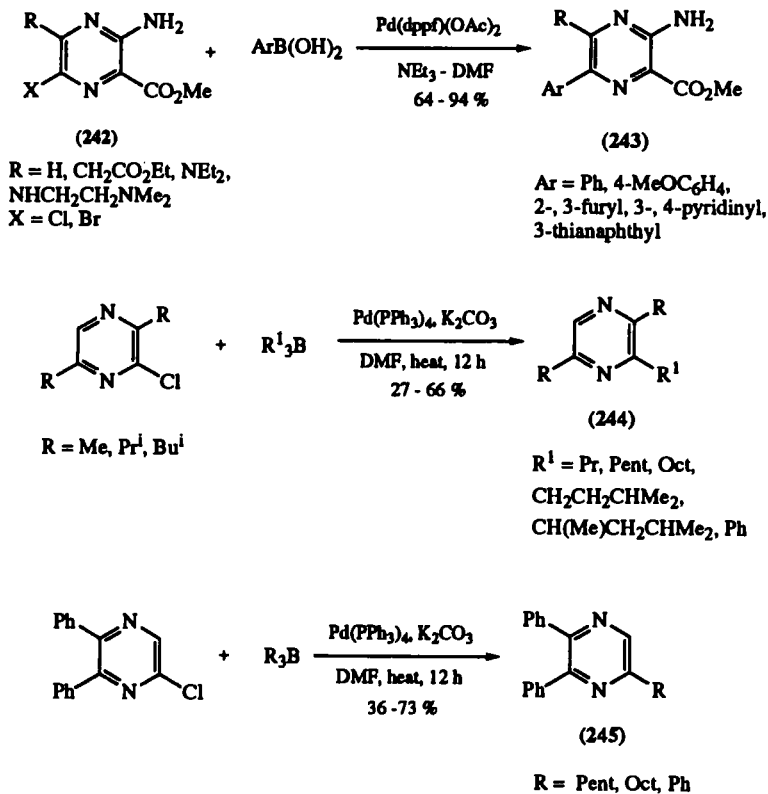


SCHEME 52

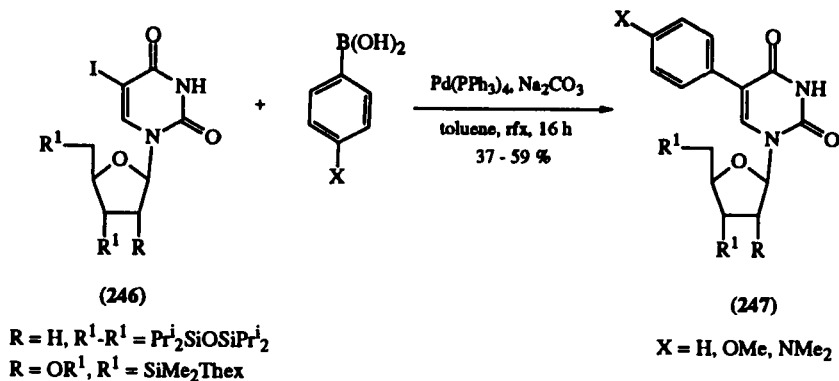
This limitation is overcome by using stannanes instead of boronic acids in the coupling reactions (see above) (91MI3).

3. Boronation and Reactions of Azinoboranes

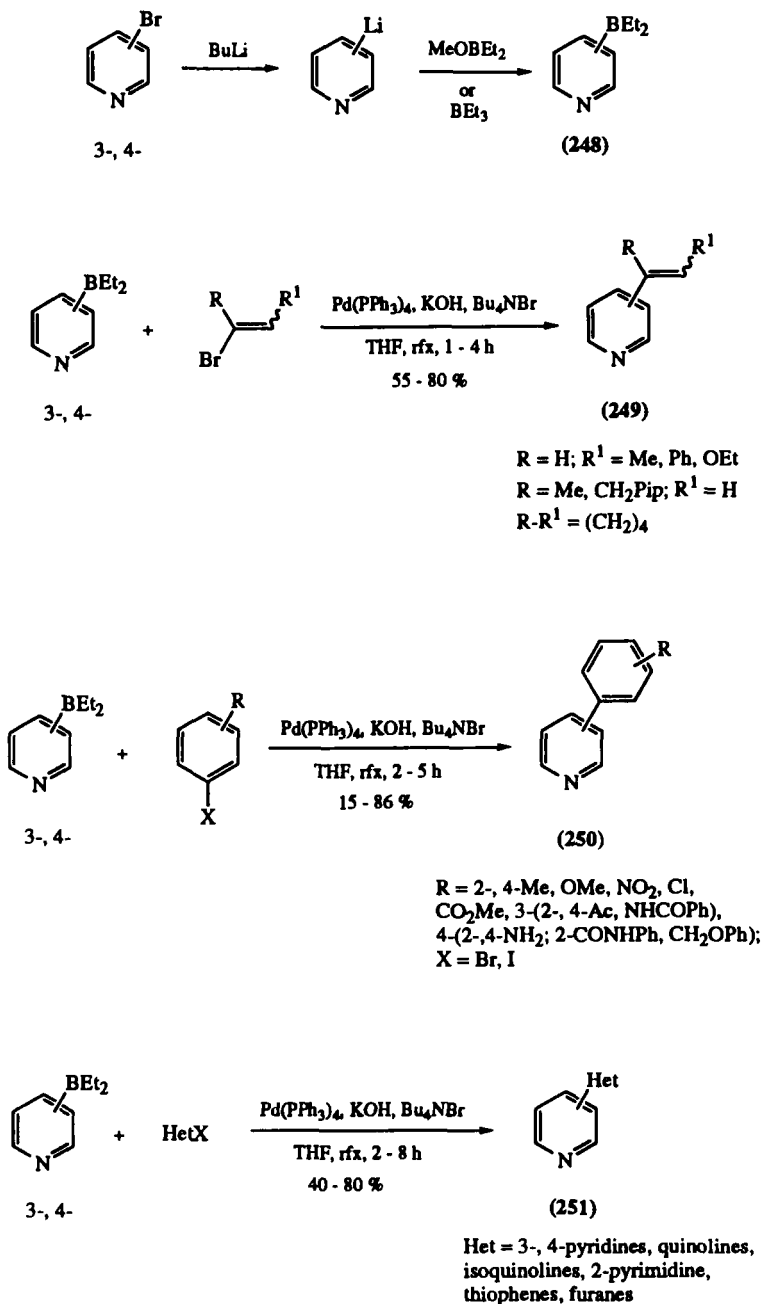
a. *Pyridine*. The azine is a constituent of the organometallic reagent to be reacted with various aryl, heteroaryl, alkenyl, or alkynyl halides and triflates in Pd-mediated reactions (Scheme 55). Pyridine is readily lithiated in its benzenoid 3-position by way of the bromide or iodide, and can also be lithiated in the 4-position via the bromide. The lithiated species reacts with triethylborane, or better with diethylmethoxyborane, to form diethyl(3-pyridyl)borane (**248**) (84H265; 84H2475; 85CPB4755).



SCHEME 53



SCHEME 54



SCHEME 55

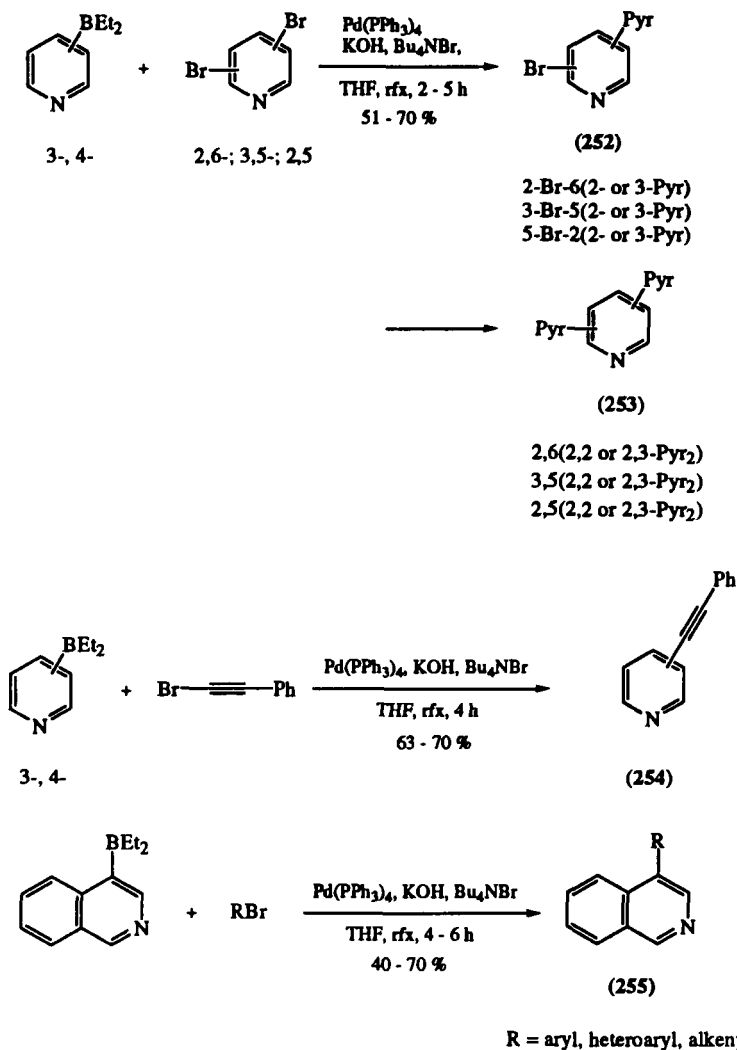
Cross-coupling of the pyridylborane (**248**) with alkenyl bromides under alkaline conditions and heating in THF proceeds well to give the alkenylated pyridine (**249**) with full regioselectivity and retention of alkene stereochemistry in both the 3- and 4-pyridine products (84H2475). Similarly, arylation with bromobenzenes affords 3- and 4-arylpyridines (**250**) in good to moderate yields, usually in the range 50–70%. The products from 2-chlorophenyl derivatives are formed in significant but low yields in both series. Iodoanilines are superior to bromoanilines in the coupling reaction (84H265; 85CPB4755). By analogy to the arylation, a number of heterocycles have been coupled to the 3- and 4-position of a pyridine (**251**) from the respective heteroaryl bromide or activated chloride (84S936; 85CPB4755).

The coupling is stepwise in symmetrical 2,6-dibromo- and 3,5-dibromopyridines (Scheme 56); the monocoupled product **252** is isolated in 51–67% yield. The predictable stepwise arylation of 2,5-dibromopyridine was observed (65–70% yield). The next step, the diarylation (**253**), allows for the use of either the diethyl(3- or 4-pyridinyl)boranes, and hence for introduction of the same pyridine or its regioisomer in the diarylation (85CPB4755).

Reactions of pyridylboranes with 1-bromo-2-phenylethyne give the alkylnylated product **254** (84H2475). An analogous series of reactions has been described in pyridine halides with diethyl(4-isoquinoliny)borane as substrate for the preparation of **255**. The reactions proceed in the same manner with comparable product yields (87H1603).

Azinoboronic acids have been prepared and applied to coupling reactions (Scheme 57). 3-Bromo- and 4-bromopyridines can be lithiated and reacted with boronates to form pyridineboronic acids, which have been coupled with methyl 5-bromonicotinate to furnish **256** when $\text{Pd}(\text{OAc})_2(\text{dppf})$ is the catalyst. Coupling with the 4-isomer has been applied to the appropriate 3-bromopyridine for the synthesis of the 4-methyl derivative (**258**) of the cardiotonic milrinone (**259**) (88JOC2052).

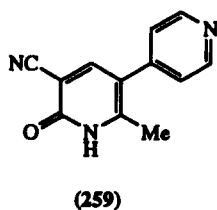
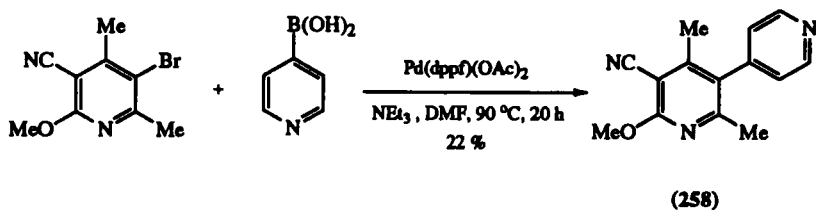
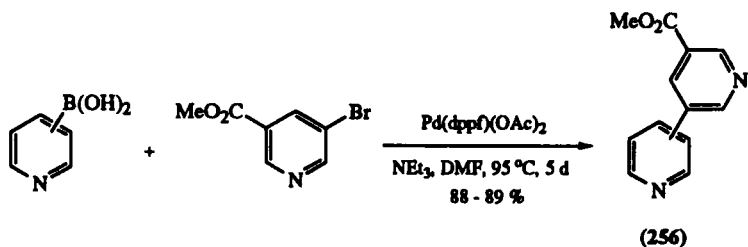
b. *Pyrimidines*. 5-Bromopyrimidines have also been lithiated and boronated (**260**) (Scheme 58). The halogen–metal exchange between 5-bromopyrimidine and butyllithium has to be carried out at low temperature (-100°C) to avoid 1:1-adduct formation with the lithiated species. The 2,4-di-*tert*-butoxy analog, however, can be lithiated in normal manner at -78°C . Boronation results from addition of tributyl borate with subsequent hydrolysis. The 5-pyrimidineboronic acids have been coupled with bromothiophenes and 3-bromoselenophene. Product (**261**) yields are comparable to the yields from the reaction with the opposite polarization, that is, with 5-bromopyrimidines and thiopene- and selenopheneboronic acid (86CS305). Using 2,4-di-*tert*-butoxypyrimidine-5-boronic acid, a number of heterocycles have since been coupled into the 5-position via bromides.



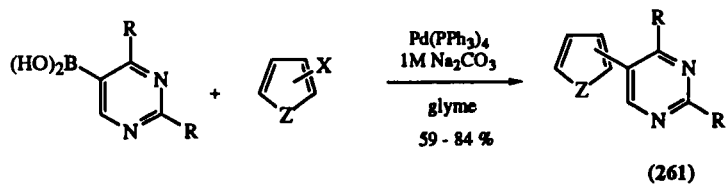
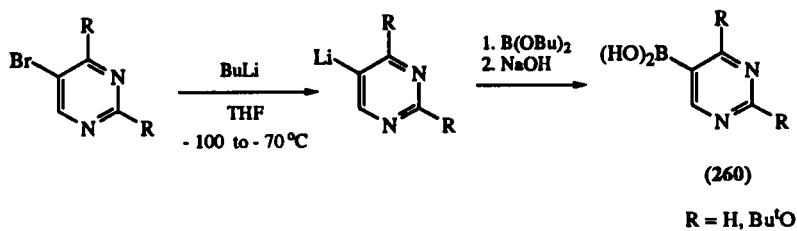
SCHEME 56

The 2-furyl derivative and the 2-thiazolyl analog of **261** are of special interest in this context because they could not be prepared by the reverse polarization procedure since furan-2- and thiazole-2-boronic acid are not readily available (90JHC2165).

The pyrimidineboronic acid has also been coupled with TMS-protected propargyl bromide (yield 32%) and with bromopropenes; the trans isomer



SCHEME 57



SCHEME 58

was the more reactive, giving the *trans*-alkenylated product in 72% yield (90JHC2165).

C. ORGANOALUMINUM COMPOUNDS

1. General

Palladium-catalyzed cross-coupling with organoaluminum derivatives in heterocycles has hitherto received modest attention. An alkenyl group in organoaluminums is readily transferable in Pd-promoted reactions. There are, however, several other good methods for transfer of alkenyl groups. But it is important that alkylaluminum compounds are promising reagents for transfer of alkyl groups to heteroarenes. Several simple alkylaluminums are commercially available. Hydroalumination, which takes place kinetically in a stereochemically fixed manner, is the most versatile route to the alkyl- and alkenylaluminum compounds used as intermediates for coupling reactions (88T5001; 91MI4).

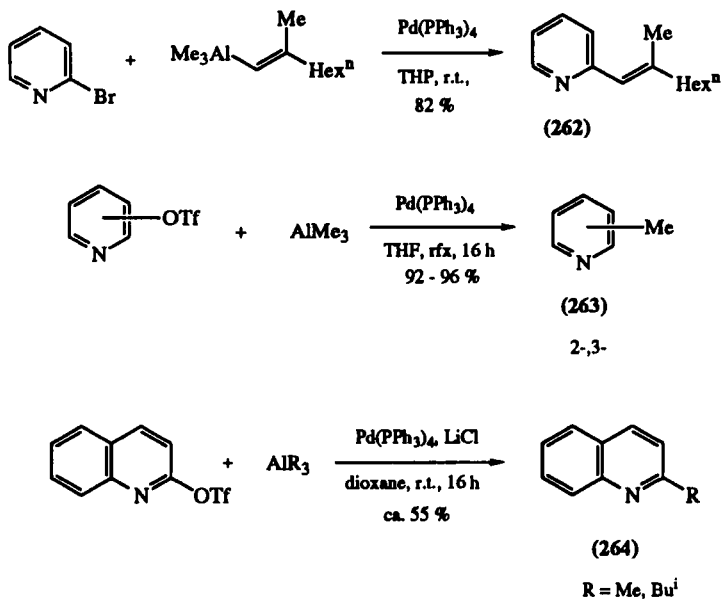
2. Halogeno- and Triflyloxy-azines

a. *Pyridine and Quinoline*. In 1982 it was reported that Pd catalyzes the reaction between 2-bromopyridine and (*E*)-(2-methyl-1-octenyl)dimethylaluminum (Scheme 59). The alkenyl group is transferred preferentially with full retention of its stereochemistry (**262**). The alkenylaluminums were prepared by the general method of zirconation of a terminal alkyne by Cp_2ZrCl_2 , followed by a metal-metal exchange reaction with trimethylaluminum (82H117).

When triflates of 2- and 3-hydroxypyridine are heated with trimethylaluminum, using $\text{Pd}(\text{PPh}_3)_4$ as catalyst, high yields of α - and β -picolines (**263**) are obtained [89JCS(P1)2513]. 2-Triflyloxyquinoline reacts with trialkylaluminums to furnish 2-methyl- or 2-isobutylquinolines (**264**) in moderate yields (89AJC279).

b. *Pyrimidine*. 5-Hydroxy-1,3-dimethyluracil, as triflate, is 5-methylated (**265**) by trimethylaluminum in high yield (Scheme 60) [89JCS(P1)2513].

c. *Pyrazine*. 2-Chloropyrazines react with trimethylaluminum to form 2-methylated products (**266**) (Scheme 60). Dimethylated products (**267**, **268**) are prepared from 2,5-dichloropyrazines and 2,6-dichloro-3,5-



SCHEME 59

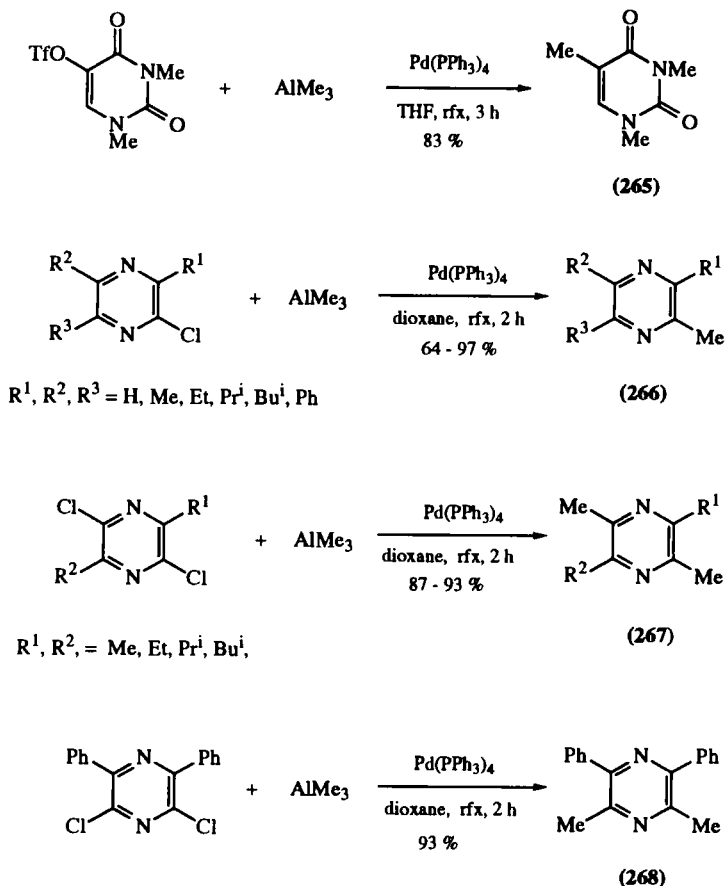
diphenylpyrazine, whereas 2,3-dichloro-5,6-diphenylpyrazine is monalkylated under the same conditions (84H2317).

d. *Purine Nucleosides.* Trialkylaluminums couple with halogenopurine nucleosides (Scheme 61). The nucleosides are persilylated before the reaction with the organoaluminum. 2-Bromoadenosine and trialkylaluminums have been used as substrates for the preparation of the alkylated nucleosides (269) in good yields, except for the isobutyl derivative (34%) where debromination was a major pathway (43%). The 6-methylpurine nucleoside (271) has been prepared by a coupling reaction between trimethylaluminum and the 6-chloropurine. Corresponding 8-alkylation reactions can be carried out starting from 8-bromopurines (92JOC5268).

D. ORGANOZINC COMPOUNDS

1. General

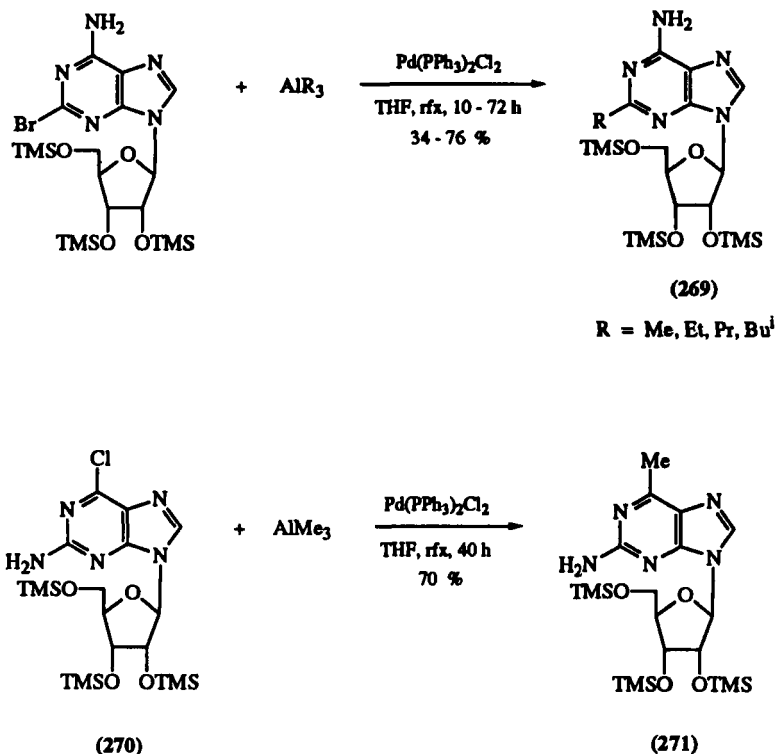
Cross-coupling of organozinc reagents with a variety of organic electrophiles using transition-metal catalysis provides an excellent method for carbon-carbon bond formation with high chemo-, regio-, and stereoselectivity (92T9577).



SCHEME 60

Organozinc compounds (R_2Zn and $RZnX$) show low reactivity in comparison with Grignard reagents owing to the highly covalent character of the carbon–zinc bond. The main application was in the Reformatsky reaction until the recent discovery of the catalytic effect exerted by transition metals on organozinc reactions. The activation to the reactive species by the transition metals is caused by transmetalation: the organozinc compound is converted into a new organometallic species of the catalyst metal, which is the reacting species in carbon–carbon bond formation.

Organozinc compounds are compatible with a wide range of functional groups in either or both of the coupling partners, an exception being hydroxyl groups, which are deprotonated. Other relatively acidic protons are tolerated in contrast to organomagnesium and organolithium com-



SCHEME 61

pounds. Zinc reagents or substrates bearing NH or NH₂ groups of amines or amides are tolerated.

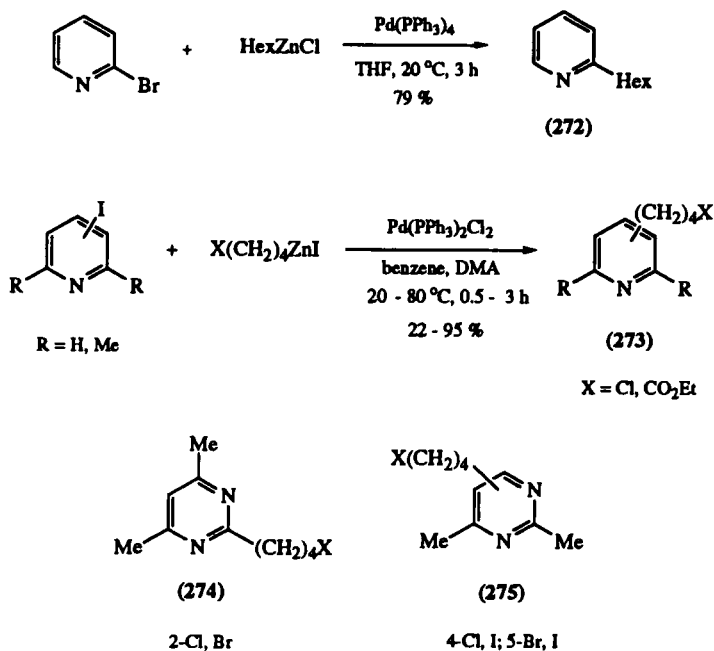
Organozinc reagents can be prepared either by a direct reaction between an organic halide and zinc metal, or by a transmetalation of the corresponding organolithium or Grignard reagents with a zinc halide. Direct insertion of halides for metallation shows predictable sensitivity to the nature of the organic moiety, the halide (Br, I), and the reaction conditions (solvent, concentration, temperature); and it is promoted by zinc activation (e.g., BrCH₂CH₂Br/TMSCl) (93CRV2117). Substrate bromides and iodides are generally the most reactive class of electrophiles. Triflates also react well.

Organozinc reagents are useful for the transfer of alkyl groups, more so than their organotin analogs. Isomerization during the alkylation reaction, or elimination reactions due to the presence of a hydrogen on a β-carbon to the metal, may lead to side reactions. Palladium catalysts are

most frequently used to effect reactions between organozinc reagents and halogeno- or triflyloxy-heteroarenes. Work has been described with alkyl- (82H117; 85CPB4309; 88S485), benzyl- (80TL4017), alkenyl- (84TL83), alkynyl- (82H117), aryl- (82H117), and heteroarylzinc compounds (87S843; 88TL5013).

2. Halogeno- and Triflyloxy-azines

a. *Pyridine*. *n*-Hexylzinc chloride has been prepared by heating a hexyl Grignard reagent with zinc chloride, then reacted further with 2-bromopyridine under the influence of Pd-catalysis to form the hexylpyridine (**272**) (Scheme 62) (82H117). Similarly, 3- and 4-iodo- or -bromopyridines and further substituted 2-, 4-, and 5-iodopyrimidines react with 4-chlorobutylzinc iodide under Pd-catalysis to form the butyl derivatives (**273–275**) (88S485). The zinc reagent was prepared from the alkyl iodide with Zn–Cu couple in benzene–DMA. Alkylzinc iodides are compatible with the presence of a carbonyl group in the substrate, in contrast to Grignard reagents.



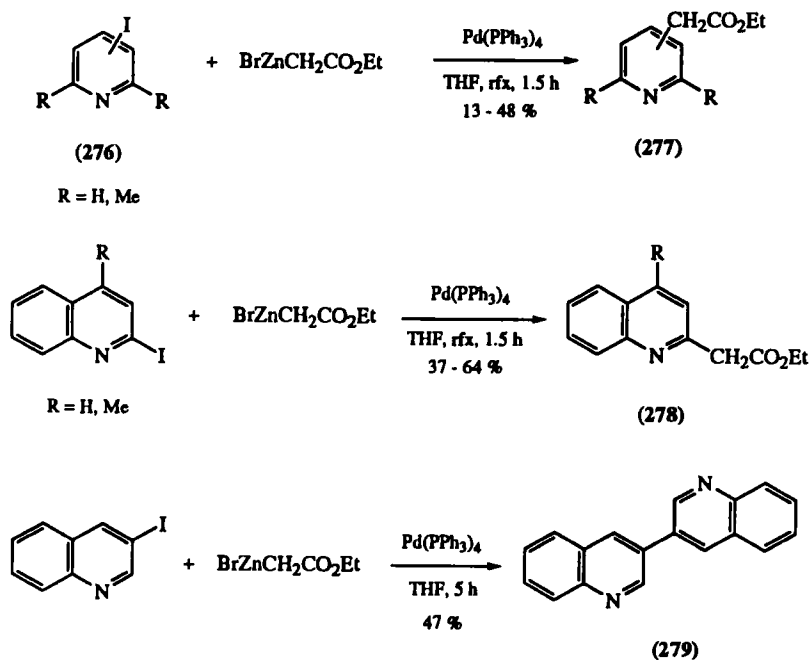
SCHEME 62

Palladium catalysis promotes the Reformatsky reaction. Heteroaryl iodides are better substrates than bromides and chlorides. Iodine in electrophilic positions in the substrate, but not in the benzenoid position, were active in the Reformatsky reaction (**277**, **278**) (Scheme 63). Homo-coupling is the major pathway for iodo derivatives in the benzenoid position, with formation of 3,3'-biquinoline (**279**) (85CPB4309).

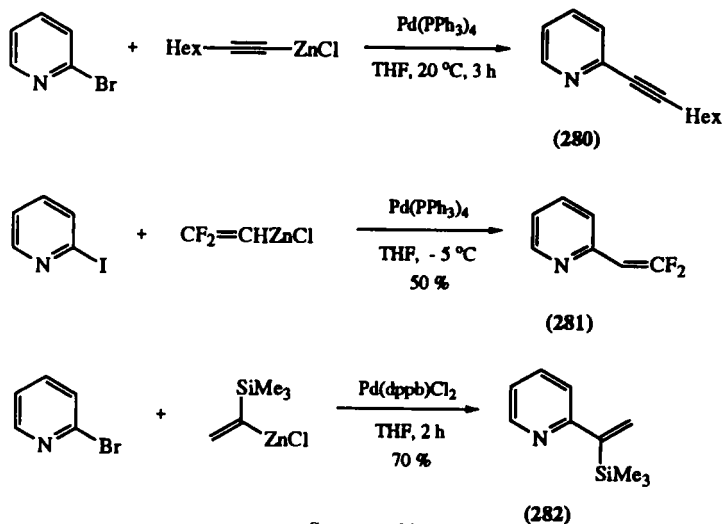
Alkynyl-heteroaryl coupling between 2-bromopyridine and 1-octyn-1-ylzinc chloride gives the 2-octynylpyridine (**280**) (Scheme 64) (82H117).

2-(2,2-Difluoroethenyl)pyridine (**281**) has been prepared by a Pd-catalyzed reaction between 2-iodopyridine and 2,2-difluoroethenylzinc chloride, which was prepared from the corresponding lithiated alkene (86S538). Similarly, the silylethenyl derivative (**282**) has been prepared from 2-bromopyridine and trimethylsilylene, which was lithiated on the α -carbon and treated with zinc chloride (84TL83).

Reactions with arylzinc substrates represent one of the most general and best routes for the preparation of unsymmetric biaryls (Scheme 65); both Ni- and Pd-complexes may be used interchangeably (77JOC1821; 88OS67). The arylzinc reagents are available by metal-metal exchange



SCHEME 63



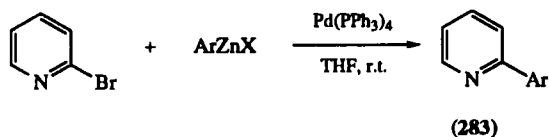
SCHEME 64

reactions with corresponding aryllithium derivatives and a zinc halide. 2-Bromopyridine and a substituted phenylzinc reagent produce heterobiaryls (**283**) in good yields (82H117). The same method can be used for preparation of 2-, 4-, and 5-(2-pyridyl)imidazoles (**284**) from *N*-alkylated or *N*-sulfonylated imidazolylzinc (88TL5013). With 5-imidazolylzinc chloride, which couples to yield (**285**), the 2-phenylthio group does not interfere with the coupling reaction. The imidazolylzinc reagents were prepared by transmetalation between lithioimidazoles and anhydrous zinc chloride.

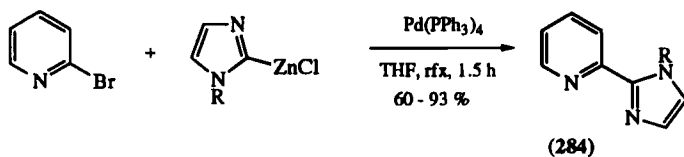
2,6-Dichloro- or 2,6-dibromopyridines react with one equivalent of benzylzinc bromide to give a 4 : 1 mixture of monalkylated (**286**) and dialkylated pyridine (**287**) (80TL845).

Triflates react similarly. The triflate of pyridin-3-ol has been coupled with 2-furylzinc chloride and Pd-catalysis to yield 3-(2-furyl)pyridine (**288**) (90SL47).

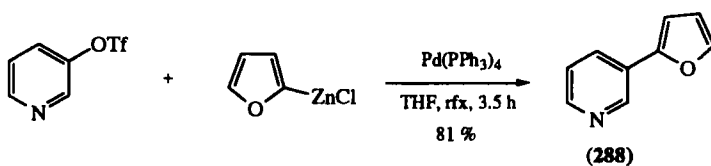
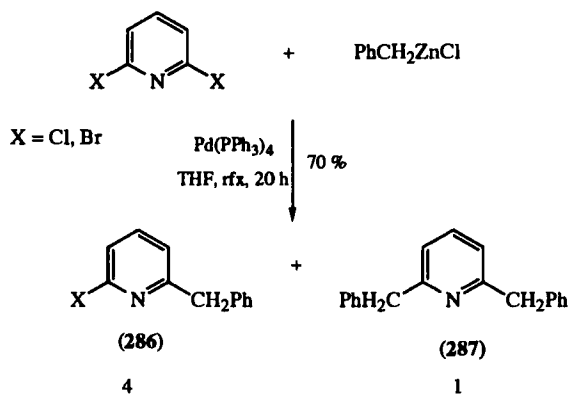
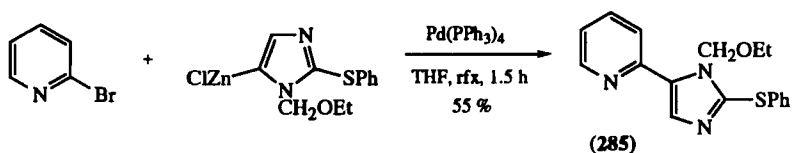
b. Pyrimidine. By analogy to the pyridines a Reformatsky reaction is feasible in pyrimidines and is exemplified by the introduction of an acetic acid unit (**289**) through substitution of a 4-iodopyrimidine (Scheme 66). In the reaction between anisylzinc bromide and 2,4-dichloropyrimidine, the 4-position is the more reactive, and the monoarylated 4-anisyl derivative (**290**) is formed using one equivalent of the zinc reagent (93H235). The regioselectivity is the same as that observed for the corresponding triflates and for Pd-catalyzed reactions of the dichloride with stannanes



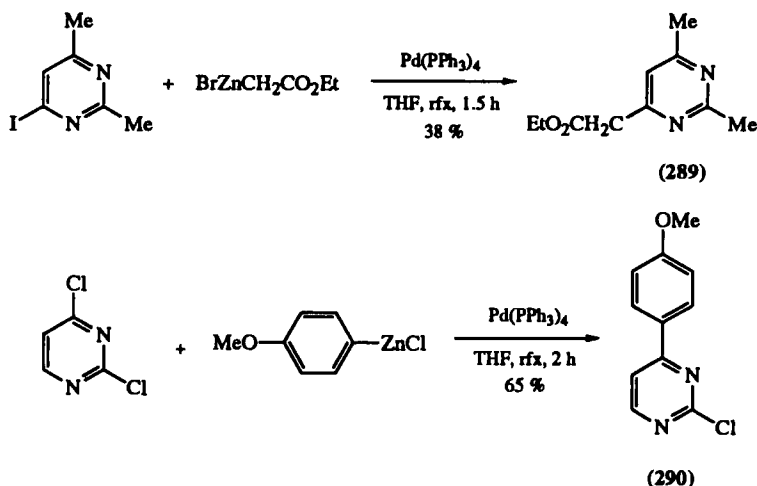
Ar = Ph, 2-, 3-MeC₆H₄,
2,4,6-Me₃C₆H₂, 2-furyl, 2-thienyl



R = Me, CH₂OEt, SO₂NMe₂



SCHEME 65



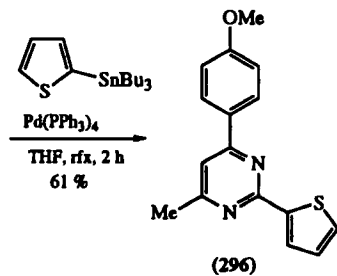
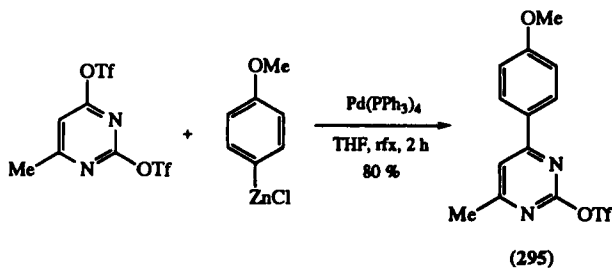
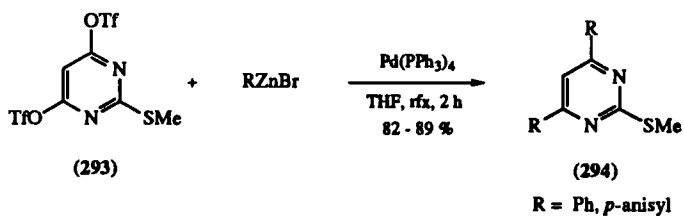
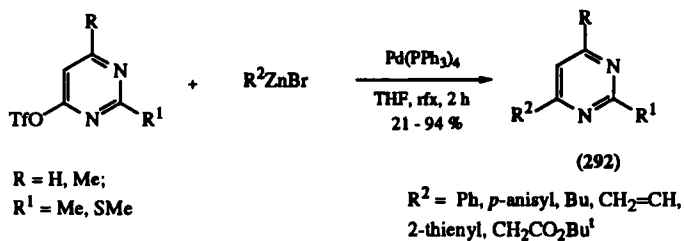
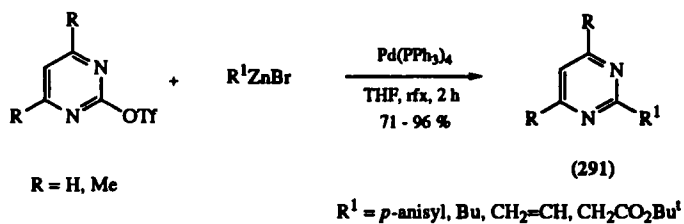
SCHEME 66

(93ACSA102). The chlorine atom in the 2-position can also be replaced by excess reagent. Another zinc or tin reagent would give a pyrimidine product with two new and different carbosubstituents.

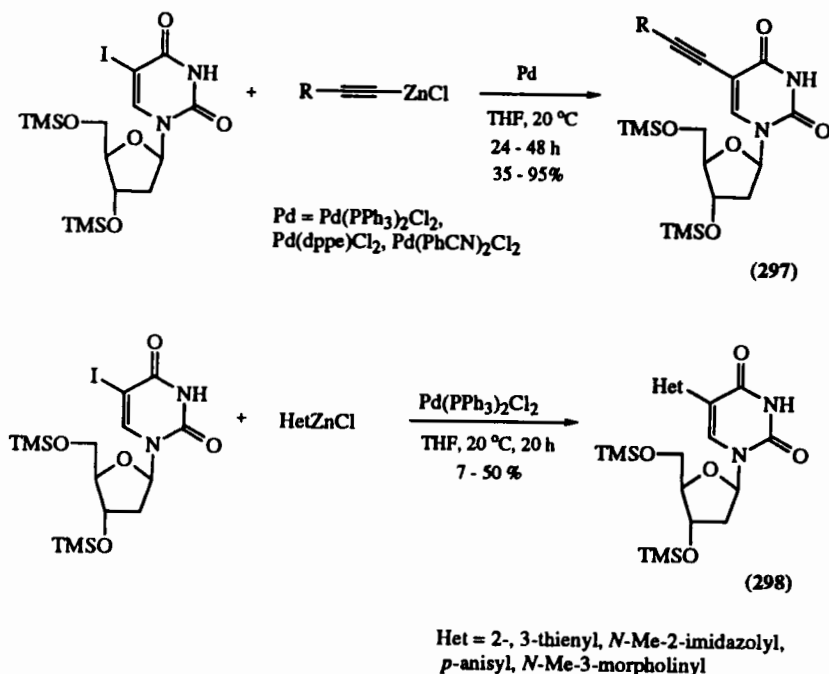
Triflates in the electrophilic pyrimidine 2- and 4-positions, as well as 2,4-ditriflates, are available from the corresponding pyrimidinones by way of triflic anhydride and a tertiary amine base (see above).

Pyrimidinyl triflates show comparable reactivity to chloropyrimidines in Pd-catalyzed reactions (Scheme 67). High yields result from coupling reactions with 2-triflyloxy- and 4-triflyloxypyrimidines (**291**, **292**). Even the Reformatsky reaction can be effected in moderate yields. Variable yields in reactions with *n*-butylzinc bromide result because of competitive olefin formation (94H501). The 4,6-ditriflate (**293**) reacts with arylzinc reagents to yield dicoupled products (**294**) (94H501). With 2,4-ditriflate the initial reaction is in the more electrophilic 4-position, as for the corresponding 2,4-dichloride. With excess *p*-anisylzinc bromide the disubstituted product is formed. The intermediate monoarylated product (**295**) has been reacted further; the second coupling with 2-tributylstannylthiophene under Pd-catalysis gives the 2-thienyl derivative (**296**) (93H235).

c. Pyrimidine Nucleosides. The coupling reaction with organozinc chlorides has been applied to substitution in 5-iodouridine (Scheme 68) (81TL945; 84TL201). A number of monosubstituted acetylenes have been lithiated and treated with zinc chloride to form alkynylzinc chlorides, which then couple under Pd-catalysis to form 5-alkynylated nucleosides



SCHEME 67



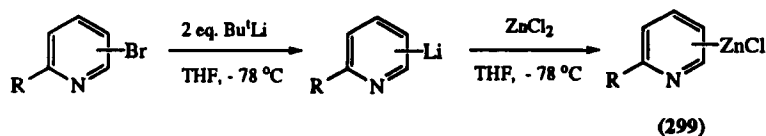
SCHEME 68

(297) (81TL945). With heteroarylzinc chlorides, 5-heteroaryluridines (298) are formed in low to moderate yields (84TL201).

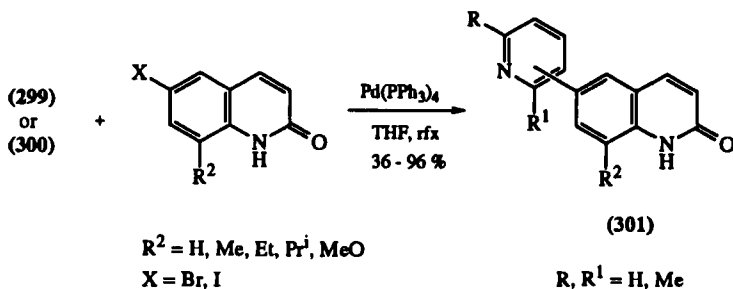
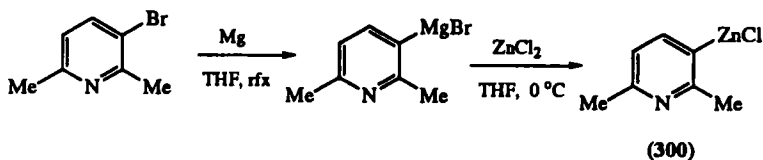
3. Zincation and Reactions of Azinozinc Compounds

a. *Pyridine*. In general, zinc reagents are prepared by a transmetalation reaction of aryllithium or arylmagnesium halides with zinc halides. The same approach is used for heteroarenes in the absence of noncompatible substituents.

In a typical reaction (Scheme 69), 2- or 3-bromo-6-methoxypyridine is lithiated in THF with *tert*-butyllithium in THF at -78°C . Low temperature and a bulky lithiating reagent are used to limit (or avoid) the tendency for adduct formation between the π -deficient heterocycles and the reagent. The lithiated species is reacted in the cold with zinc chloride to form the zincated derivative (299). 3-Bromo-2,6-dimethylpyridine, a benzenoid bromide, is zincated by heating in THF with magnesium, and the metal-metal exchange is effected by zinc chloride (300). The pyridylzinc chlorides can be coupled with 3-bromo- or iodo-2-quinolines using Pd-



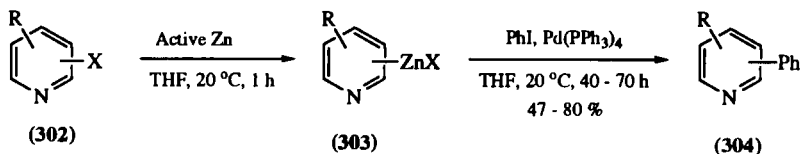
R = H, OMe



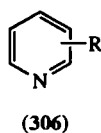
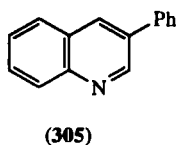
SCHEME 69

catalysis; the yields of pyridylquinolines (301) are generally good. Since the reactions in the examples described were run on unprotected quinolinones, at least two equivalents of the organometallic reagent had to be used (87S843).

The direct synthesis of arylzinc halides from the halide and activated zinc (90TL4413; 91JOC1445) can also be applied to heteroaromatic systems (93TL9713), in particular to the direct preparation of π -deficient heteroarylzinc halides (Scheme 70). Bromo- and iodopyridines react well with activated zinc at room temperature to form the metallated species 303. The coupling of phenyl iodide with the pyridines is relatively slow. 3-Iodopyridines gave considerably higher yields than their bromo analogs in this reaction; the yield from 3-iodoquinoline was 96% of the 3-phenyl product (305). Alkoxy carbonyl-substituted pyridylzinc halides (302) can be zincated and coupled without attack on the ester group. Unsymmetric as well as symmetric biheteroarenes (306) can be assembled by appropriate choice of substrates.

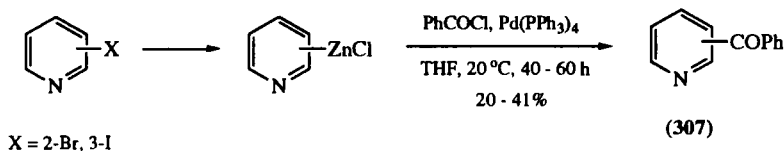
R = H, 2,6-Me₂, 4-CO₂Et

X = 2-Br, 3-Br, 2-I

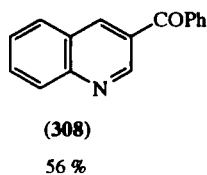


53 - 84 %

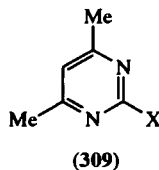
R = 2-(2,6-dimethyl-4-pyrimidinyl)
 = 2-(3-pyridinyl)
 = 2-(3-quinolinyl)
 = 3-(2-quinolinyl)
 = 3-(2,4-dimethyl-6-pyrimidinyl)



X = 2-Br, 3-I



56 %

X = I
= Ph

SCHEME 70

Ketones are formed from pyridylzinc halides on acylation with acid chlorides or anhydrides; in reactions with benzoyl chloride or benzoic anhydride, pyridyl ketones (307) are formed in moderate yields. Reactions with 3-iodoquinoline gave the 3-benzoyl derivative 308. Organostannanes may be a better choice for ketone formation (see above).

b. *Pyrimidine*. In the electrophilic pyrimidine 2-position zincation and coupling of the iodo derivative (**309**) took place to the extent of 26% (93TL9713).

E. ORGANOMAGNESIUM COMPOUNDS

1. General

Heterocyclic sulfides and thiols are generally readily available substrates either from cyclization or substitution reactions. The sulfur functionality can be useful for carbosubstitution using nickel catalysis together with Grignard nucleophiles. The nature of the ligands surrounding the metal catalyst, a low-valent nickel species, is important for the outcome of the reaction with alkyl Grignard reagents, especially secondary alkyls. With $\text{NiCl}_2(\text{PPh}_3)_4$ competition between H-transfer and alkyl-transfer to the heterocycle occurs. With H-transfer the heterocycle is reduced, and the alkyl group of the Grignard reagent is expelled as an olefin (82CC840). This reaction is suppressed by using 1,3-bis(diphenylphosphino)propane (dppp) for ligation of the catalyst, as in reactions with butyl and cyclohexyl derivatives (85JOC1125).

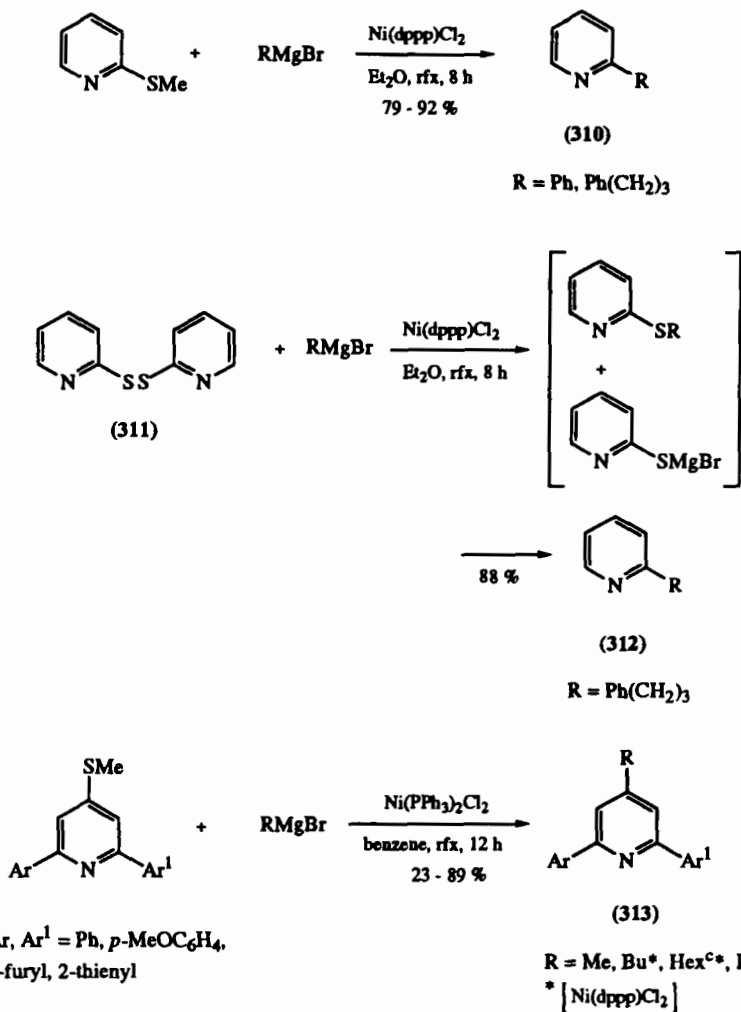
The primary application of Grignard reagents in coupling reactions with nickel promotion is with organic halides. Cross-coupling under the influence of nickel catalysis is not, however, limited to Grignard reagents; organic complexes of lithium, aluminum, zinc, and zirconium are also active (82MI2).

2. Sulfenylazines

a. *Pyridine and Quinoline*. Nickel-promoted reactions between organomagnesium derivatives and thiated pyridine in the 2-position give carbosubstitution products (**310**) (Scheme 71) (79CL1447). Disulfides (**311**) are cleaved by organometallic reagents, including Grignard reagents. The products from the cleavage are substrates for the subsequent coupling reactions (**312**) (79CL1447).

2,6-Diaryl-4-methylthiopyridines are substituted in the 4-position by hydrogen, alkyl, and aryl groups via nickel-induced Grignard reactions (**313**) (85JOC1125).

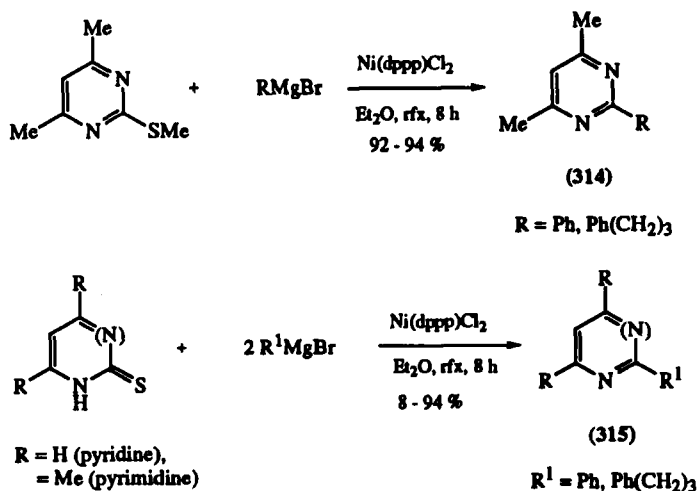
b. *Pyrimidine*. Grignard reagents readily form 1:1 adducts with π -deficient azines. This can be avoided when the electrophilic positions are occupied as in 2-methylthio-4,6-dimethylpyrimidine; substitution is in the



SCHEME 71

2-position (314) (Scheme 72). With a free thiol group two equivalents of the Grignard reagent is required, as exemplified by the preparation of 315 (79CL1447).

c. *Purine*. The methylthio group in 6-methylthiopurines is located in an electrophilic position and can be substituted by Grignard reagents either by reduction or carbosubstitution (316) using Ni-catalysis and reflux in



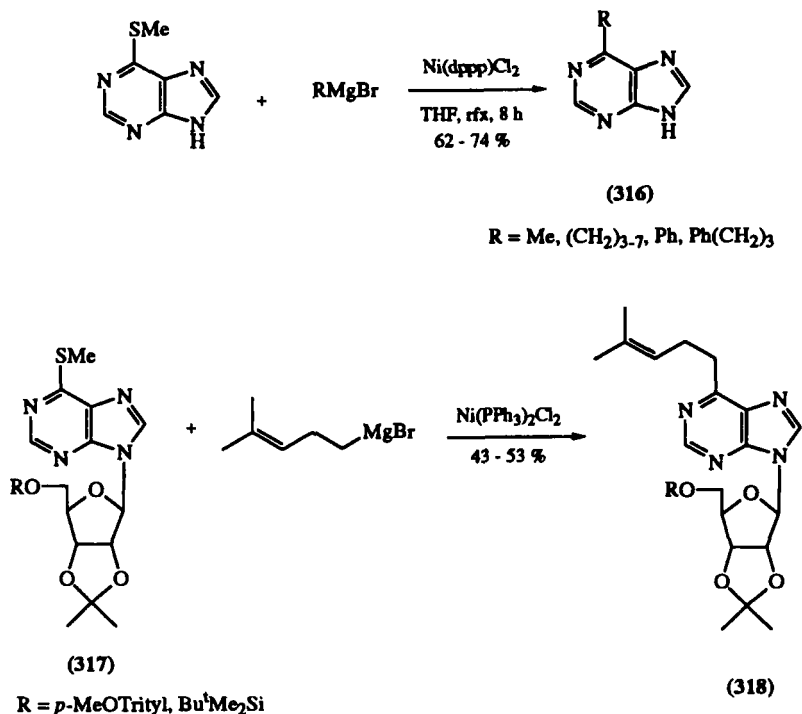
SCHEME 72

THF. An abnormal effect of phosphine ligands on the reaction was observed in this case—triphenylphosphine was far superior to dppp for the substitution reaction (85BCJ664).

d. *Purine Nucleoside.* Thiated nucleosides react similarly to the parent purine. The 6-methylthiopurine nucleoside (317) can be alkylated in the 6-position (318) by this method (85BCJ664).

3. Halogenoazines

a. *Pyridine.* In 1973 it was reported (73JHC243) that the chlorine atom in 2-chloroquinoline could be replaced by alkyl groups from Grignard reagents in Ni-mediated cross-couplings (325). Pyridine reacts in the same manner (75JHC443), as seen in the coupling reactions (319) of 2-chloro- or 2-bromopyridine. A chlorine atom in the 3-position is less readily replaced, and hence 3-bromo derivatives are used (75JHC443; 82T3347). A methyl group ortho to the halogen increases the steric interaction, which results in decreased yields; methyl groups in other positions do not affect the coupling (320) (75JHC443). Both chlorine substituents in 2,6-dichloropyridine are replaceable (321). Even the benzenoid chlorines in 3,5-dichloropyridine have been replaced by butylation in moderate yield (322) (82T3347). Coupling of 2,6-dichloropyridine with bis-Grignard reagents can be used for the construction of macrocycles, as in the prepara-

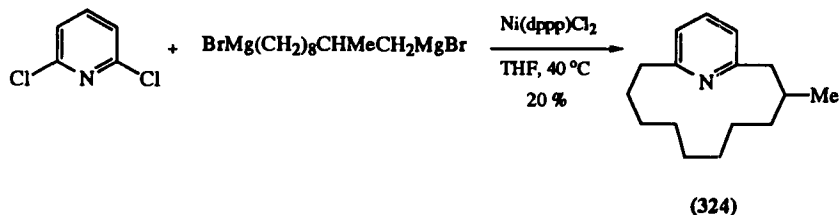
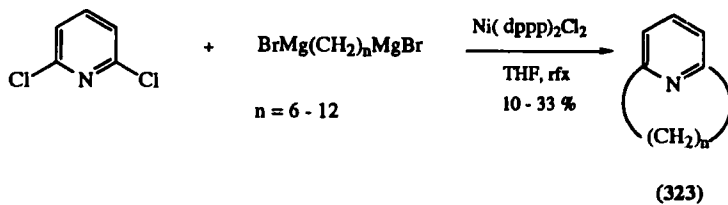
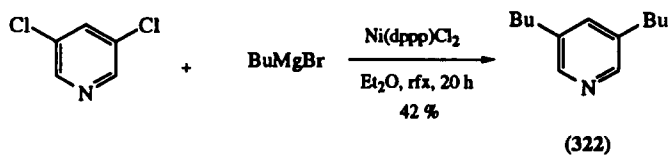
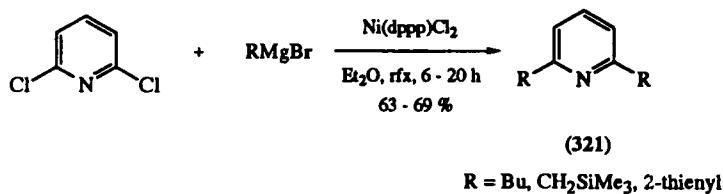
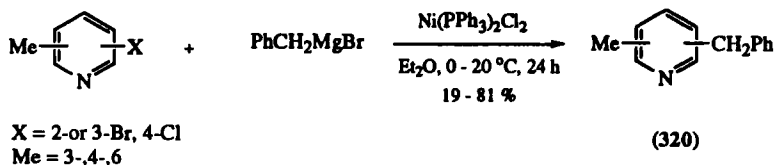
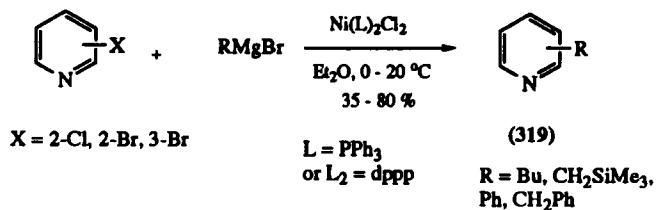


SCHEME 73

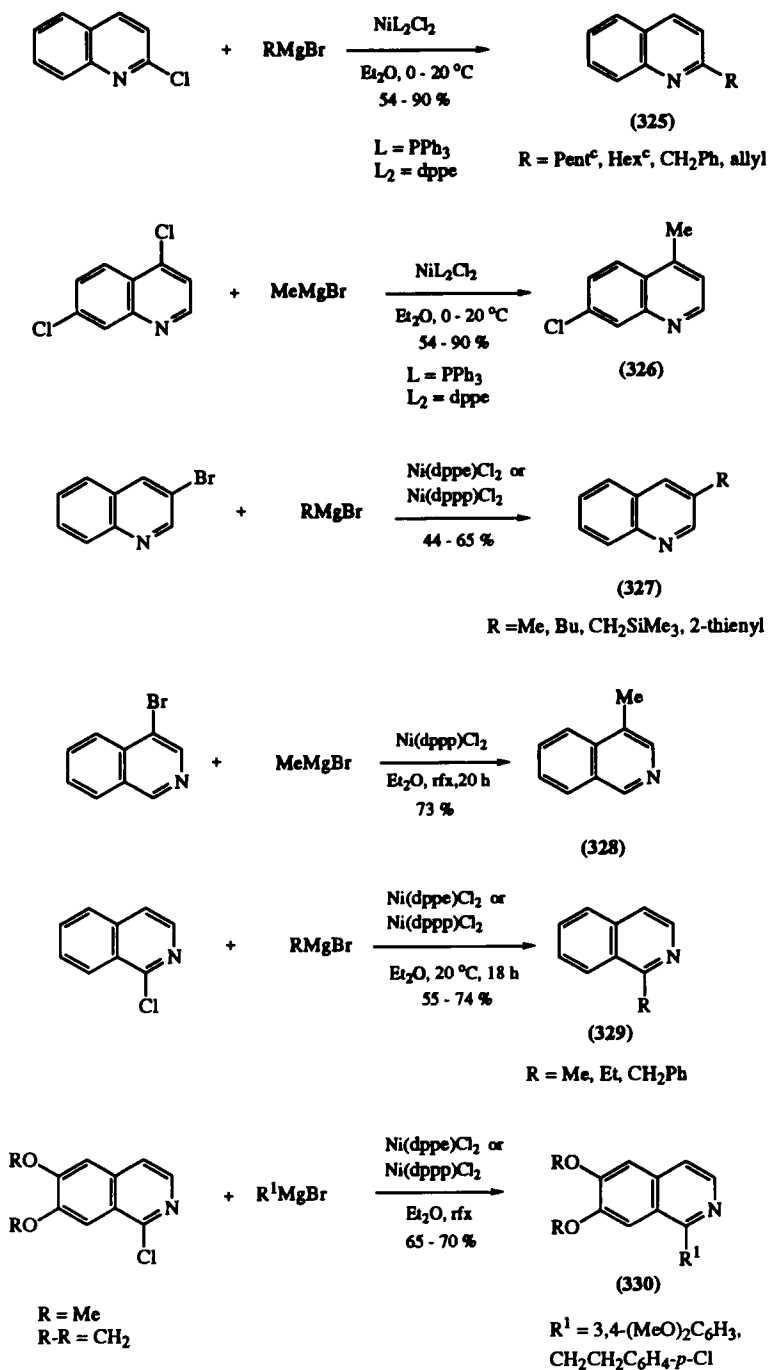
tion of $[n](2,6\text{-pyridinophanes})$ (323) such as muscopyridine (324) (75JA4405; 80PAC669).

Early studies on the coupling reactions of quinolines (73JHC243) showed that, as in the alkylation of 2-chloroquinoline with Grignard reagents in Ni-mediated reactions (325), the course of the reaction was ligand-dependent. It was claimed that for benzyl and allyl Grignard reagents, PPh_3 was better than 1,2-bis(diphenylphosphino)ethane (dppe). The latter promoted homo-coupling at the expense of hetero-coupling from the Grignard reagent. When the Grignard reagent contains a β -hydrogen on a saturated carbon, dppe is the ligand of choice. In contrast, olefin elimination with reduction of the heterocycle is a significant or dominating reaction with the PPh_3 ligand. However, dppp has become the most commonly used ligand in recent work.

In 4,7-dichloroquinoline the chlorine in the electrophilic 4-position, and not in the benzenoid 7-position, is substituted selectively by the Grignard methyl group (326). A bromine in the benzenoid 3-position in

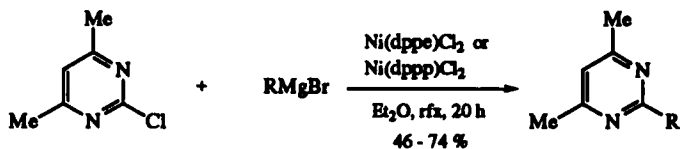


SCHEME 74

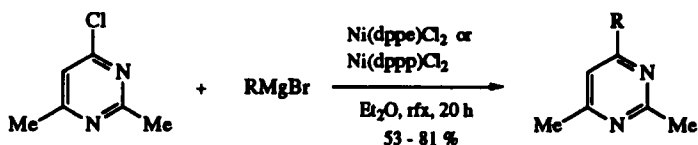


SCHEME 75

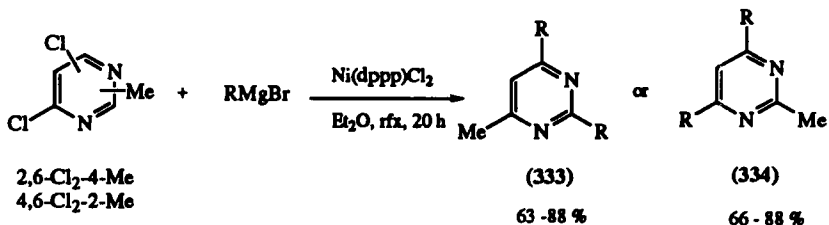
quinoline, however, is readily replaced (327) (73JHC243; 82T3347). 4-Bromoisoquinoline is methylated in the 4-position (328) by methylmagnesium iodide. Isoquinoline is substituted in the 1-position (329) using 1-chloroisoquinoline. Isoquinoline precursors (330) for the synthesis of alkaloids have been constructed from appropriately substituted 1-chloroisoquinolines (82T3347) by this method.



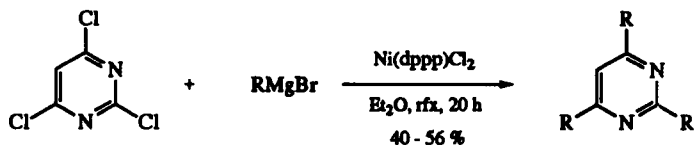
(331)

R = Et, Bu, Pent, Hex, Ph, CH₂Ph

(332)

R = Et, Bu, Pent, Hex, Ph, CH₂Ph2,6-Cl₂-4-Me
4,6-Cl₂-2-Me

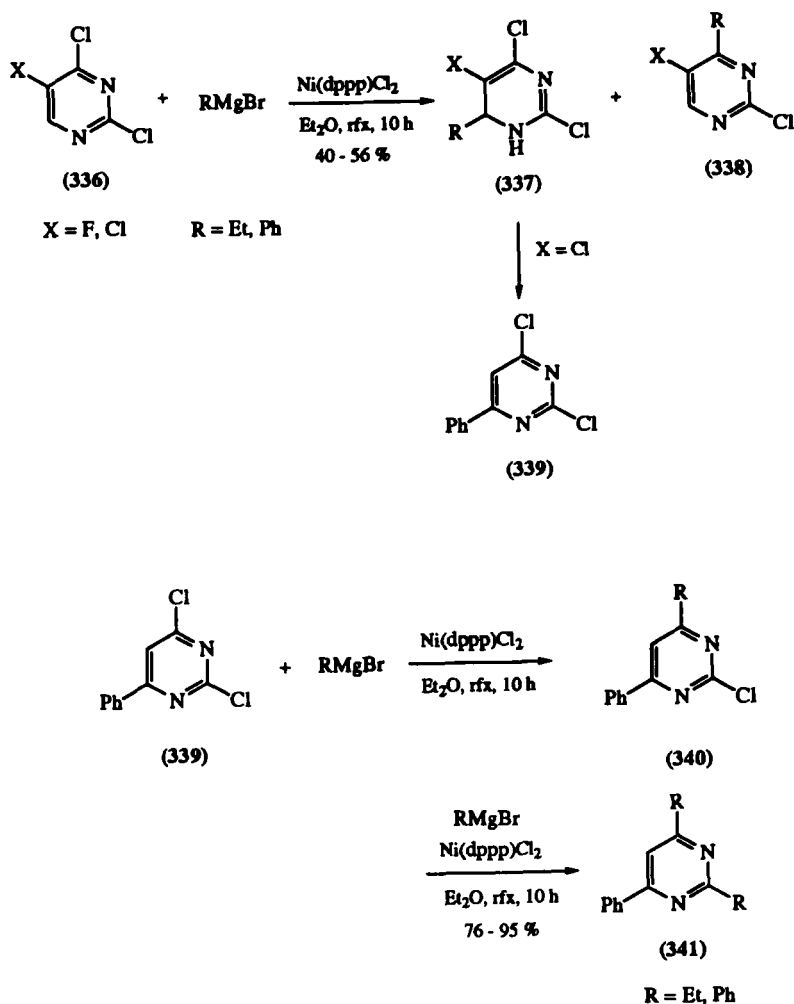
R = Me, Et, Ph



(335)

R = Et, Ph

b. *Pyrimidine*. Reactions in pyrimidines are very much of the same type (78CPB2160). The chlorine in an electrophilic 2- or 4-position is readily exchanged by carbosubstitution (331, 332), and the 2,4- and 4,6-dichloro derivatives become disubstituted (333, 334). With chlorine atoms in all the electrophilic positions, trisubstitution (335) results with excess reagent. The regiochemistry is difficult to control using one equivalent of Grignard reagent; 2,4,6-trichloropyrimidine gave a mixture of the trisubsti-



SCHEME 77

SCHEME 78

d. *Purine Nucleosides*. In purine nucleosides 6-chloro derivatives are suitable intermediates for carbo substitution reactions, as exemplified by the preparation of nucleoside **345** (Scheme 79) (82TL4191).

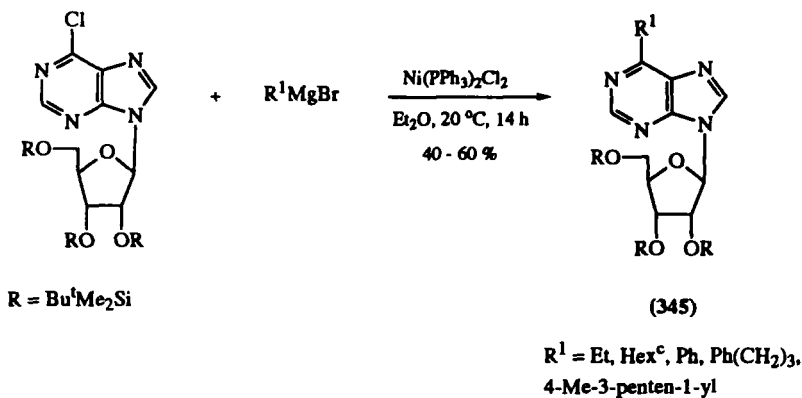
F. ORGANOCOPPER COMPOUNDS

1. General

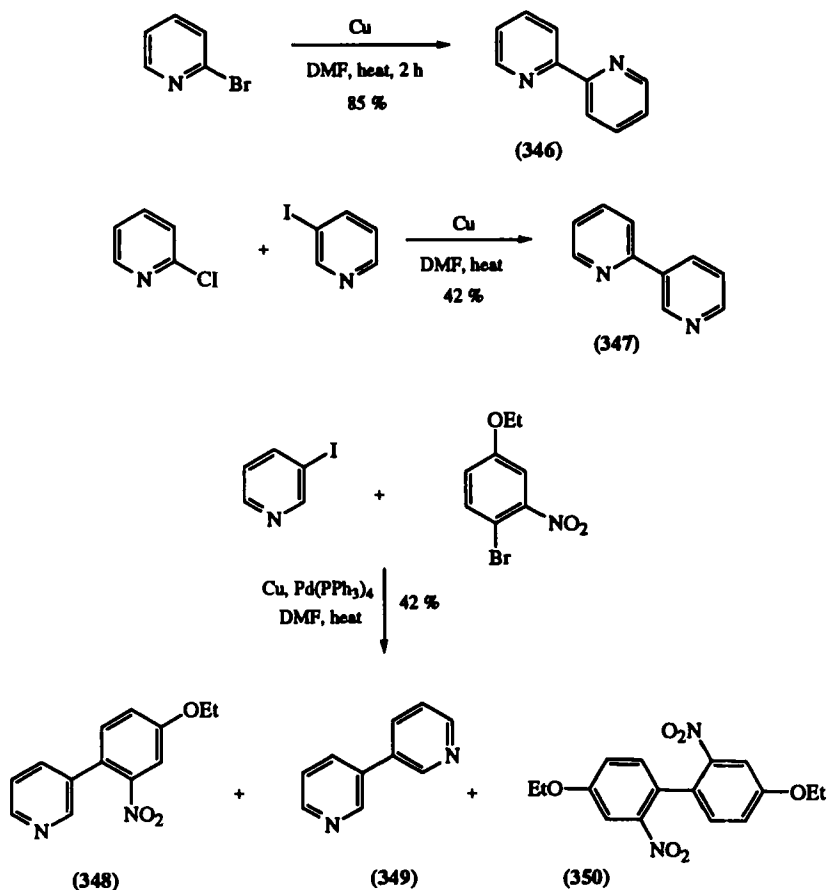
Palladium- or nickel-catalyzed coupling reactions have in the last couple of decades surpassed by far the importance of Cu-mediated coupling reactions in arene and heteroarene systems. Even so, many important synthetic reactions are copper-mediated (82MI2). The Ullman reaction is a copper-promoted homo- or hetero-coupling between two aryl halides (74S9). The reaction requires heating with finely divided copper powder. Another useful reaction for the preparation of alkynyl derivatives of arenes is the Stephens-Castro reaction, which is a coupling reaction between an aryl iodide and a copper(I) acetylide, most frequently in pyridine or DMF [63JOC2163; 63JOC3313; 66JOC4071; 69JCS(C)2453].

2. Halogeno- and Triflyloxy-azines

a. *Pyridine*. Dimethylformamide has been found to be a good solvent in the Ullman reaction for the preparation of 2,2'-bipyridine (**346**) from 2-bromopyridine (Scheme 80) (65CA18018). With two different substrates, a mixture of two homo-coupled dimers and the cross-coupled product is



SCHEME 79



SCHEME 80

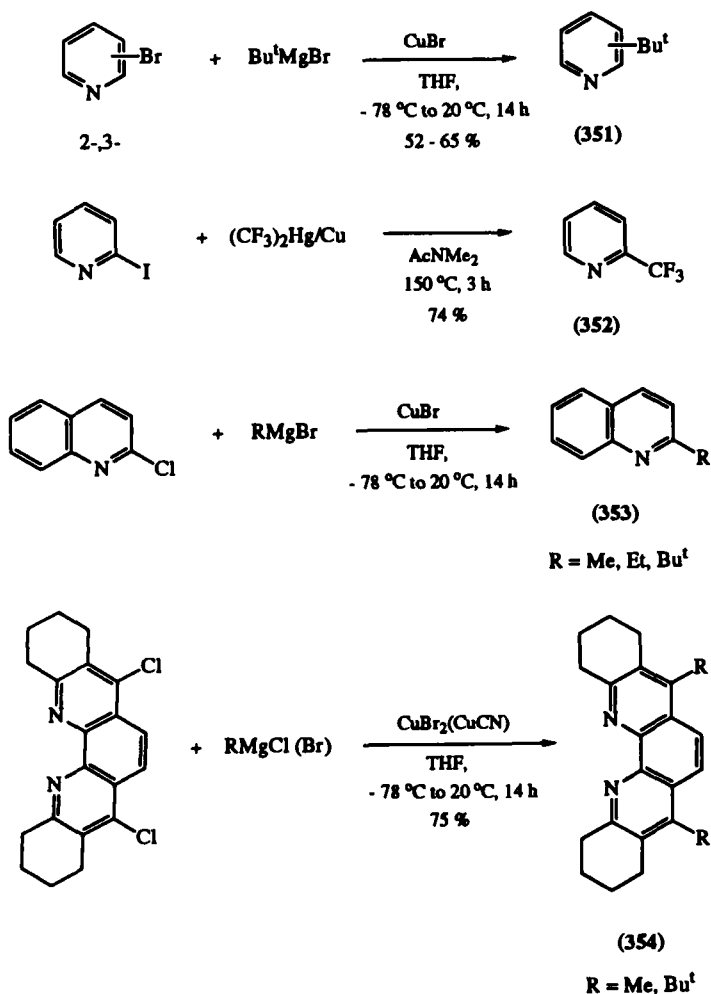
formed, unless there is an optimal difference in reactivity between the two substrates. 2-Chloropyridine and 3-iodopyridine give the cross-coupled product 2,3'-bipyridine (**347**) (71CA53433).

Palladium catalysis has been found to promote the Ullman reaction, and may also influence the course of the reaction. Under typical Ullman conditions homo-coupling (**349**, **350**) is favored in the reaction between 3-iodopyridine and bromo-nitrobenzenes, whereas the presence of $\text{Pd}(\text{PPh}_3)_4$ favors cross-coupling (**348**). Both 2- and 4-iodopyridines and 2-bromopyridine undergo Pd-mediated coupling (84JOC5237; 93TL3421).

Copper-mediated alkylation or alkenylation has been used widely in arenes but is rarely applied to π -deficient heteroarenes. Aliphatic Grignard

reagents react in the presence of copper bromide (Scheme 81); a *tert*-butyl group is substituted into 2- and 3-positions of the pyridine (**351**) via the respective bromide and, together with other alkyls, into the quinoline 2-position (**353**) via its chloride.

Trifluoromethylation of aliphatic and aromatic halides can be effected with a Cu-reagent which is prepared by heating bis(trifluoromethyl)mercury and copper powder together. The 2-trifluoromethylpyridine (**352**) can be prepared in this manner from 2-iodopyridine (80S932).

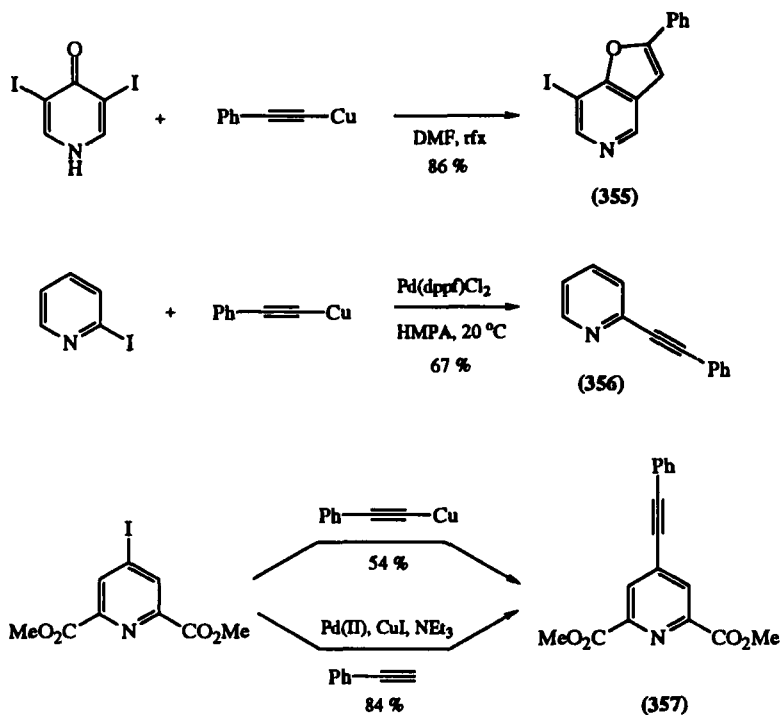


SCHEME 81

An alternative alkylating agent, which is derived from an alkyl Grignard reagent and Cu_2Br_2 or CuCN in a 2:1 ratio, has been used in reactions with azine chlorides in electrophilic positions (e.g., a 5,8-dichlorophenanthroline) (**354**) and bromides. This method also gives reasonable yields of both ethyl and *tert*-butyl pyridines (87JOC3847).

Alkynyl derivatives have been prepared by the Stephens–Castro reaction (Scheme 82). 3,5-Diiodo-4(1*H*)-pyridinone without *O*-protection is monocoupled with phenylethynylcopper. The 5-alkynyl product subsequently suffers Michael attack from the vicinal oxygen function to form a fused product, a furo[3,2-*c*]pyridine (**355**) [66JOC4071; 87ACSA(B)219; 89JCS(P1)1165].

The Stephens–Castro reaction generally requires heating in high-boiling solvents, but the reaction conditions can be substantially moderated by addition of a Pd-catalyst. Thus 2-iodopyridine is alkynylated (**356**) with phenylethynylcopper at room temperature with Pd-catalysis (82DOK1138).



SCHEME 82

A coupling reaction that does not involve prior preparation of a Cu(I) acetylide is provided by Pd-catalyzed cross-coupling of aryl halides with acetylenes in the presence of CuI. The 4-alkynylated product (**357**) was obtained from the corresponding 4-iodo derivative in 84% yield using Pd-catalysis, and in 54% yield from preformed Cu(I) acetylide without catalysis [87ACSA(B)219].

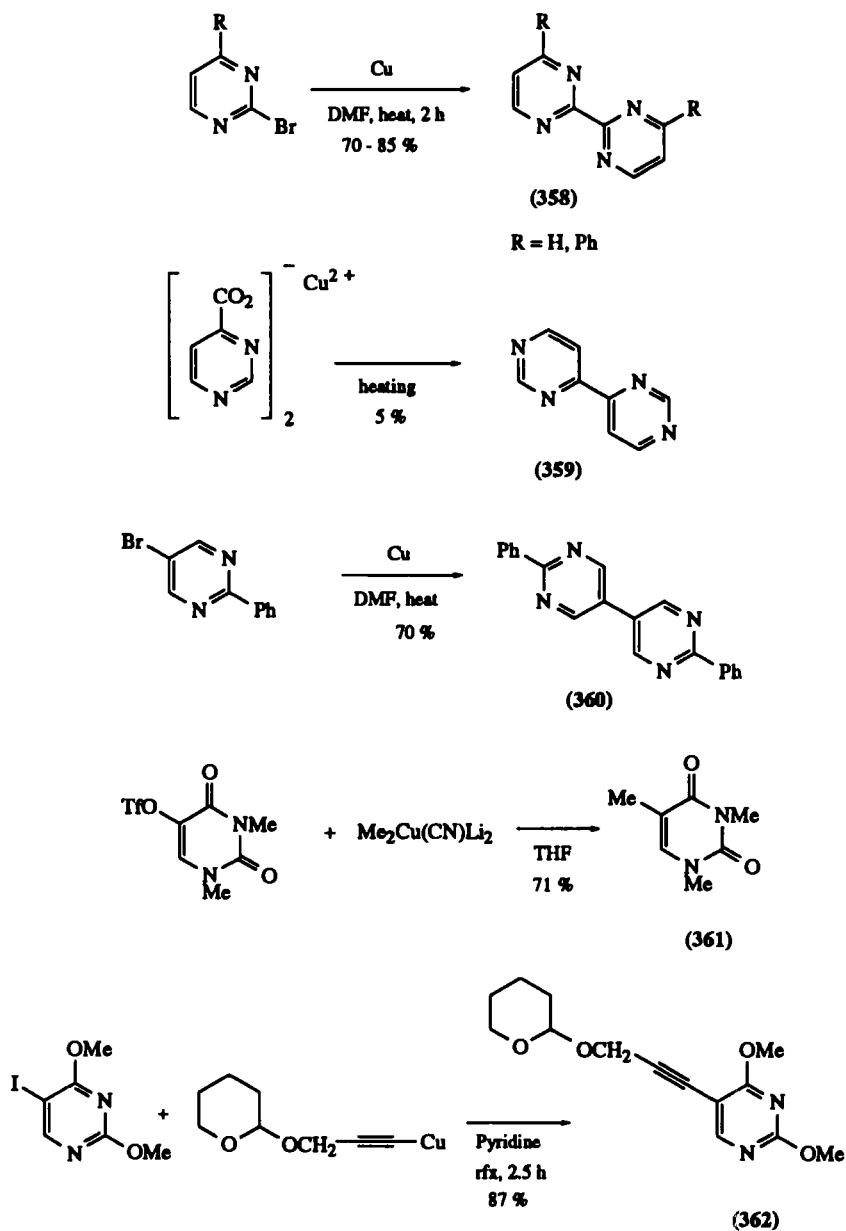
b. *Pyrimidine*. 2,2'-Bipyrimidine (**358**) (62JOC2945) and 4,4'-diphenyl-2,2'-bipyrimidine (67JOC1591) can be prepared from the corresponding 2-bromopyrimidine by Cu-mediated reactions on heating in DMF (Scheme 83). 4,4'-Bipyrimidine (**359**) has been prepared by pyrolysis of the copper(II) salt of pyrimidine-4-carboxylic acids; 2,2'-bipyrazine has also been prepared by pyrolysis of the Cu(II) salt of pyrazine-2-carboxylic acid (7%) (67JOC1591).

Coupling can be effected in all positions. Reactions between different positions correspond to cross-coupling. In 5-bromopyrimidine, coupling occurs between two benzenoid positions (**360**) [67JCS(C)1204]. In Cu-mediated alkylation, the 5-triflyloxy group in the uracil derivative can be substituted by a methyl group for preparation of the corresponding thymine (**361**) using the higher-order cuprate $\text{Li}_2\text{Cu}(\text{CN})\text{Me}_2$. Coupling with the butyl homolog $\text{Li}_2\text{Cu}(\text{CN})\text{Bu}_2$, however, gave a mixture of the expected 5-butyl derivative (20%), the 6-butyl isomer (10%), and the uracil, which formed by a reductive process (87H355).

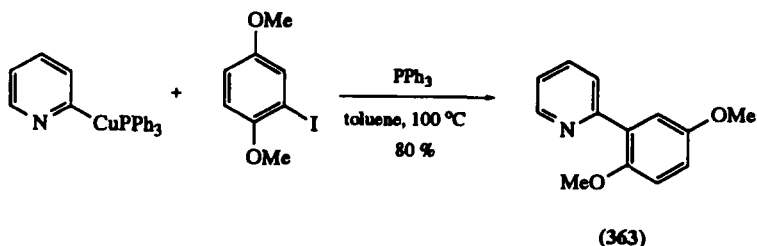
In the Stephens–Castro reaction *O*-methylated 5-iodouracil has been reacted with THP-protected propargyl alcohol as a Cu-derivative to give the 5-alkynyl product (**362**).

3. Cupration and Reactions of Azinocopper Compounds

Pyridine. Cross-coupled products can be prepared after metallation of either substrate. Initial metallation and coupling was used in the formation of **363** (Scheme 84). Copper–halogen exchange, however, may lead to substantial amounts of symmetric biaryls. Addition of triphenylphosphine to the reaction mixture stabilizes 2-pyridylcopper, preventing thermal decomposition to 2,2'-bipyridine and the copper–halogen exchange responsible for formation of symmetric biaryl. 2-Pyridylcopper is prepared by lithiation of 2-bromopyridine with subsequent metal–metal exchange with Cu(I) iodide. The copper reagent has been used to prepare the coupling product (**363**) from iodobenzenes. Similar couplings can be used in reactions with 3-pyridylcopper as substrate (86T3981; 87CS519).



SCHEME 83



SCHEME 84

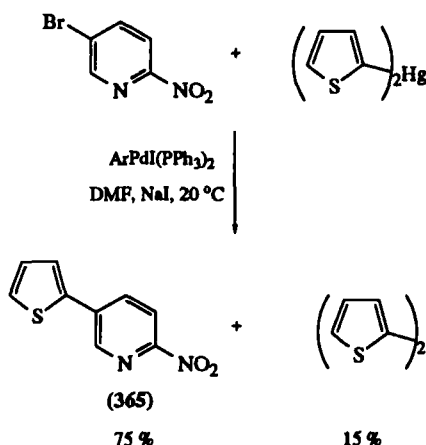
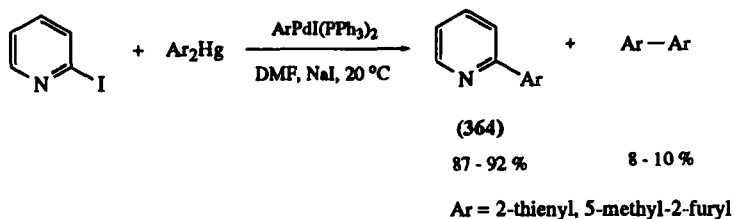
G. ORGANOMERCURY COMPOUNDS

1. General

The reactivities of organomercurials make them useful reagents in organic synthesis; they are stable toward hydroxylic solvents and air. However, their importance is dwarfed by their high toxicity and low solubility in general. Organomercurials are available by electrophilic substitution reactions in appropriate substrates or by metal-metal exchange reactions. The product from electrophilic substitution is frequently used as an intermediate for metal-metal exchange reactions to furnish another organometallic reagent. In general, Pd-mediated cross-coupling reactions with organic halides or their equivalents provide an efficient method for selective carbon-carbon bond formation (82TL1713; 85MI1).

2. Halogeno- and Triflyloxy-azines

Pyridines. The Hg-Pd coupling method has been little explored in azines. Biheteroaryls (364) are formed in Pd-mediated reaction under mild conditions between 2-iodopyridine and organomercurials (Scheme 85). 5-Bromo-2-nitropyridine is thienylated (365) by the same type of reaction. Small quantities of homo-coupled products are present in both cases. The Pd-catalyzed cross-coupling reactions of organomercurials may proceed with low selectivity owing to catalytic demercuration of organomercurials. Sodium iodide may be added to the reaction mixture because the iodide ion shifts the selectivity of the reaction toward the cross-coupling product and retards the oxidative demercuration process [89JOM(364)C231].



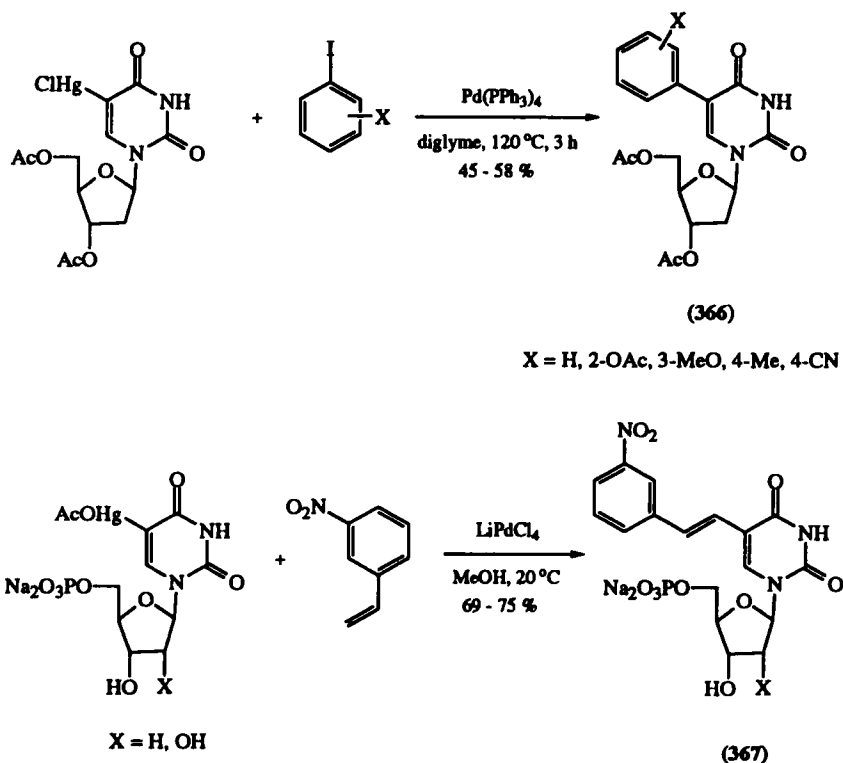
SCHEME 85

3. Mercuration and Reactions of Azinomercurials

Pyrimidine Nucleosides. Most of the studies of azine mercurials have been in the field of nucleosides, especially on carbosubstitution of mercurials in the 5-position in pyrimidine nucleosides derived from uracil and cytidine.

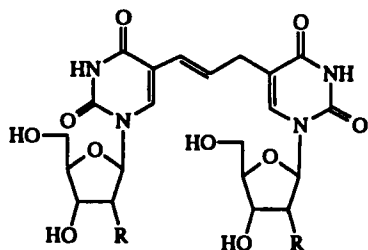
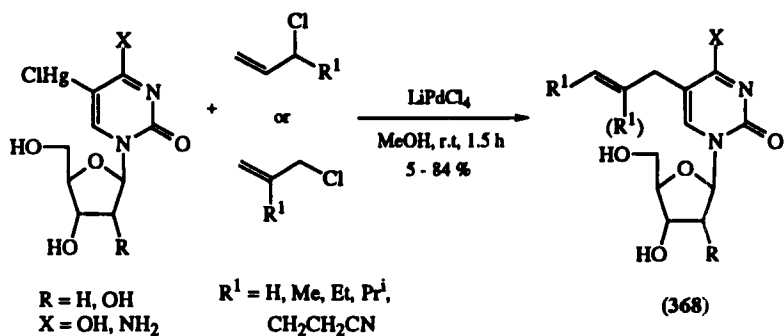
Pyrimidine nucleosides are readily attacked by electrophiles, such as Hg(II) acetate in the pyrimidine 5-position. The anion is subsequently changed to halide. Thus 2'-deoxyuridine has been mercurated by Hg(OAc)₂ in aqueous methanol and coupled with iodobenzene or substituted derivatives on heating with diglyme in a Pd-mediated reaction with formation of 5-aryl derivatives (366) (Scheme 86). The acetate is used for solubility reasons (84TL2431).

m-Nitrostyrene and *p*-nitrostyrene are good acceptors for the Heck coupling and form the trans products of 5-(2-phenylethenyl)uridine and 2'-deoxyuridine derivatives (367) (79TL1653).

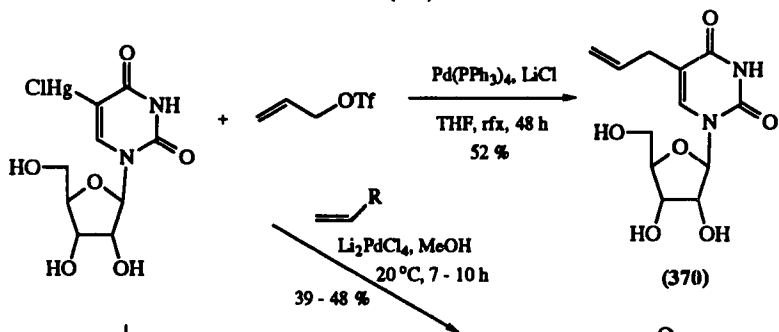


SCHEME 86

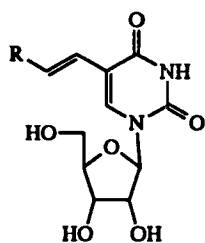
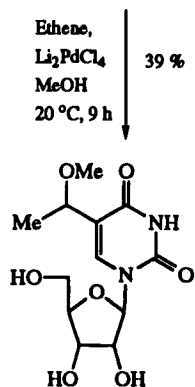
5-Chloromercury derivatives of 2'-deoxycytidine, cytidine nucleosides, and the uridine analogs can be allylated in the 5-position (**368**) in reactions in methanol with an allyl chloride under the influence of Li_2PdCl_4 as added catalyst (Scheme 87). Preferential reaction is on the allylic carbon most remote from the chloro-attached carbon, and the minor product has the opposite regiochemistry. Both olefinic stereoisomers are formed, but the predominant product has the trans configuration (**368**). In the reactions of allyl chloride the bridged 5,5'-nucleoside (**369**) is also formed. Presumably, the metal in the palladized heterocycle complexes the double bond of the initial coupling product (**368**), and this is followed by reductive elimination (78JOC2870; 81JOC1423). Reactions of allylic alcohols and their acetates are slower, and the products are inferior in quality and yields. The course of the reaction has been rationalized as an initial mercury-palladium exchange followed by addition of the palladized heterocycle to the alkene and HCl elimination. When allylation of 5-



(369)



(370)



$R = CO_2Me, Ph$

chloromercuryuridine is run in THF with allyl triflate and excess LiCl under Pd-catalysis, the allylated product (**370**) is obtained without the dicoupling observed above (91CJC198).

In methanol the initially ethenylated product from 5-chloromercuryuridine or -deoxyuridine and ethene can add methanol to form the corresponding 5-(1-methoxyethyl)uridine (**371**). Styrene and methyl acrylate, which are good acceptors for the Heck coupling, are used for alkenylation to form the trans products (**372**) (78JA8106).

H. ORGANOMAGNESIUM COMPOUNDS IN REACTIONS WITH SULFINYLAZINES

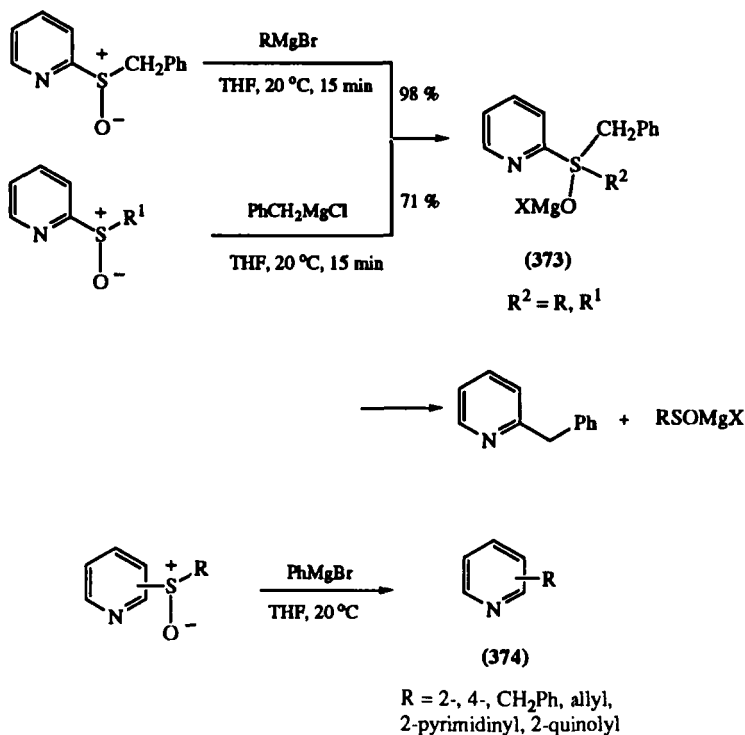
1. General

Nucleophilic substitution in electrophilic azine positions with nonstabilized carbanionic reagents is difficult. It has been found, however, that sulfoxides derived from an electrophilic azine position can react with a Grignard reagent with replacement of the sulfinyl group and carbosubstitution [90AHC(48)1].

2. Organomagnesium Reactions with Sulfoxides

Pyridine and Quinoline. In reactions with benzyl derivatives the same product—2-benzylpyridine (Scheme 88)—was formed from either benzyl 2-pyridyl sulfoxide and phenylmagnesium bromide, or phenyl 2-pyridyl sulfoxide and benzylmagnesium iodide [84TL69; 87JCS(P2)405]. Other examples include 2-allylpyridine from allyl 2-pyridyl sulfoxide and phenylmagnesium bromide, and 2-allylquinoline from methyl 2-quinolyl sulfoxide and allylmagnesium chloride (89BCJ2338). The course of these reactions is rationalized as a ligand coupling in an intermediate σ -sulfurane [90AHC(48)1]. After the initial addition of the Grignard reagent to the sulfinyl group (**373**), by analogy to a carbonyl group, the relative migratory aptitude of the substituents decides the nature of the coupling product. Benzyl and allyl groups migrate selectively to the electrophilic carbon in the pyridine 2-position. 4-Sulfinylpyridine and 2-sulfinylpyrimidine react in the same manner (**374**), but the reaction failed for the benzenoid 3-sulfinylpyridine. The ligand coupling in the σ -sulfurane is a concerted process since optically active sulfoxide with methylmagnesium bromide was coupled with full retention of stereochemistry [87JCS(P2)405].

In the absence of groups with high migratory aptitude, the reaction takes another course. Simple alkyl 2-pyridyl sulfoxides react with phenyl-

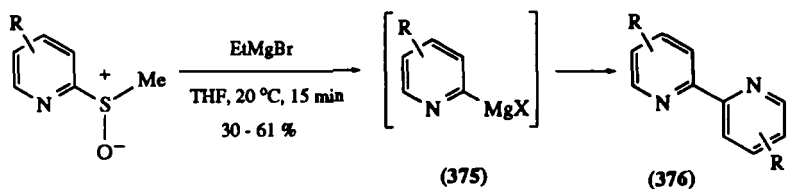


SCHEME 88

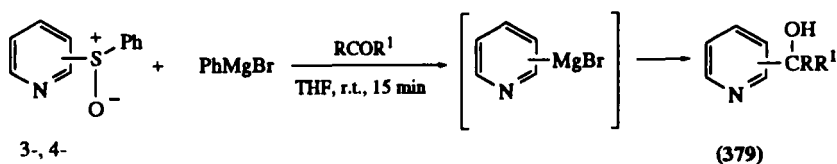
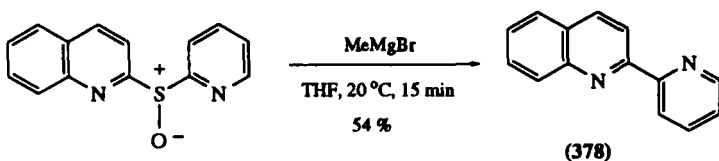
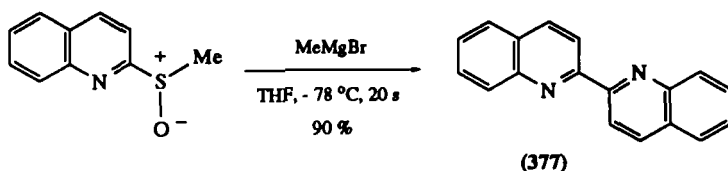
magnesium bromide or lower alkyl Grignard reagents to form homo-coupled 2,2'-bipyridine (376). The reaction is fast at room temperature and is rationalized as an exchange of ligands in the initially formed σ -sulfurane followed by expulsion of 2-pyridylmagnesium halide (375). The metallated pyridine adds to another pyridyl sulfoxide with subsequent elimination as 2,2'-bipyridine. The intermediacy of metallated pyridine was shown in a trapping experiment with benzaldehyde. This constitutes a simple method for the preparation of homo-coupled 2,2'-bipyridines (87PS123). The coupling reaction is even faster for 2-quinoline derivatives (377).

In cross-coupling reactions mixtures of products are avoided by having the desired ligands in the same sulfoxide, demonstrated by the reaction of 2-pyridyl 2-quinolyl sulfoxide (378) (89BCJ2338; 89BCJ3848).

The intermediate 2-pyridylmagnesium bromide reacts so fast with sulfoxides that it is trapped only in part by the presence of carbonyl compounds. The slower reactions of the Grignard intermediates from 3- and



R = H, SMe, Cl, Br



R = Ph, α -naph, *p*-anisyl, furyl, styryl

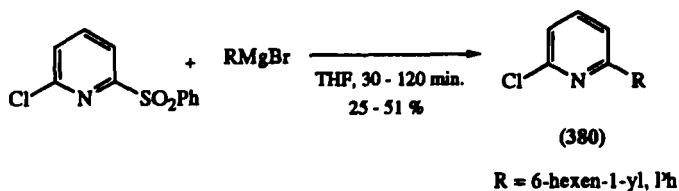
R^1 = H

R-R¹ = cyclic, acyclic, sat., unsat.

SCHEME 89

4-pyridine derivatives and 4-quinoline derivatives allow for addition reactions to aldehydes and ketones (379) (86TL3899).

Sulfonyl groups in electrophilic positions can be substituted directly by Grignard reagents. Phenyl sulfones have been used to avoid proton abstraction from the reagent by the Grignard reactant. Chemo-selective displacement of the sulfonyl group in preference to a chlorine substituent, both in electrophilic positions, has been observed (380). In 4-phenylsulfonylpyridine, reactions with aryl Grignards gave some substi-



SCHEME 90

tution, and with alkyl Grignards 4,4'-bipyridine was a major product (86H3337).

IV. Homo-Coupling

A. NICKEL CATALYSIS IN REACTIONS OF HALOGENOAZINES

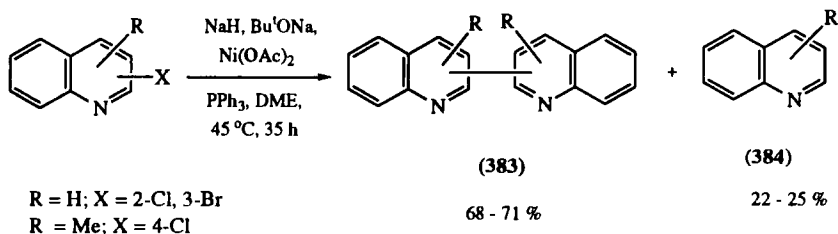
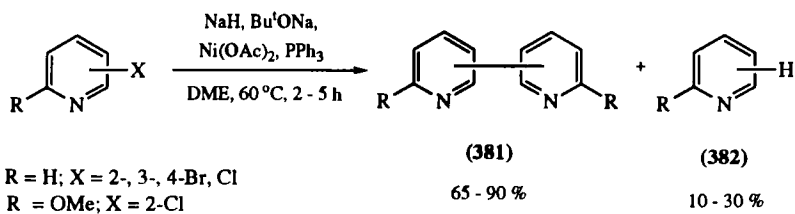
1. General

Biphenyl and biheteroaryl compounds can be prepared by transition-metal-promoted reductive coupling of aryl or heteroaryl halides. Nickel catalysis is common. At least in the heterocyclic field, zinc is the most widely used metal for reduction of nickel salts into highly reactive low-valent nickel species, which promotes coupling by oxidative insertion into the carbon-halogen bond. Two pathways have been suggested, one in which the key step is reduction of Ni(II) to Ni(0) (77TL4089), and the other in which Ni(II) is reduced to Ni(I) (86JOC2627). Other protocols for the reduction of Ni(II) salts include the use of the metals Mg or Mn (86JOC2627), and the use of NaH in the mixture NaH/*tert*-BuONa/NiOAc)₂/PPh₃ (88TL5483).

2. Low-Valent Nickel-Catalyzed Homo-Coupling

Pyridine, Quinoline, and Isoquinoline. Using a protocol consisting of NaH/*tert*-BuONa/Ni(OAc)₂/PPh₃ (Scheme 91), the binary compounds **381** and **383** are formed in good yields irrespective of the relative position of the halogen in the azine (Scheme 91). The by-products (**382**, **384**) of this protocol arise from hydrogenolysis of the heteroaryl halides.

Protocols for zinc reduction of nickel salts seem to be preferable (84S736). The coupling, mediated by the reagent formed in situ from zinc metal and Ni(II)-phosphine complexes, generally proceeds in high yields (**385**–**388**) (Scheme 92) (84S736). In some cases, minor amounts of by-



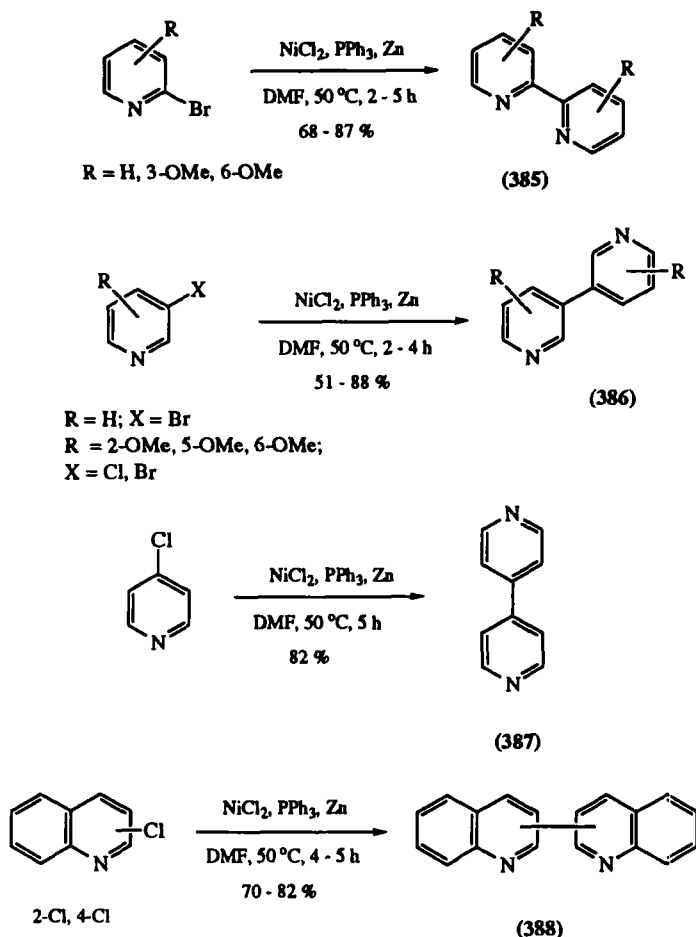
SCHEME 91

product arise by hydrogenolysis of the halide. In a study of homo-coupling reactions of 2-bromo-3-methoxypyridine using the protocols Zn–Ni, the Ullman Cu–DMF coupling at 150°C, or Pd-charcoal gave the coupling product **385** in 75, 25, and 18% yield, respectively (84S736).

In the presence of iodide ions, added to the reaction mixture as Et_4NI , the Zn–Ni coupling reaction can be run in THF with heterocyclic chlorides, bromides, or iodides to form **389–391**. Since bipyridines tend to make stable complexes with nickel, 0.3 equivalents of $\text{NiBr}_2(\text{PPh}_3)_2$ was used for the halopyridines together with excess zinc as the reducing metal. Oxo groups (aldehydes, ketones, esters) do not interfere in this coupling of halides (90BCJ80).

Dihydroxybipyridines (**392**) can be prepared by the Zn–Ni protocol without protection of the phenolic hydroxy group, but in most reactions the hydroxy groups have been protected as methyl ethers (**393**) (90S279). 2-Bromopyridin-3-ols as well as 3-bromoisquinolin-4-ol were homo-coupled (**392**, **394**). The product from the homo-coupling of 2-bromoquinolin-3-ol had poor solubility characteristics, and therefore the *O*-methyl derivative was a better substrate for the subsequent product (**393**) isolation; the methyl protecting group is removed from the product under acidic conditions (90S279).

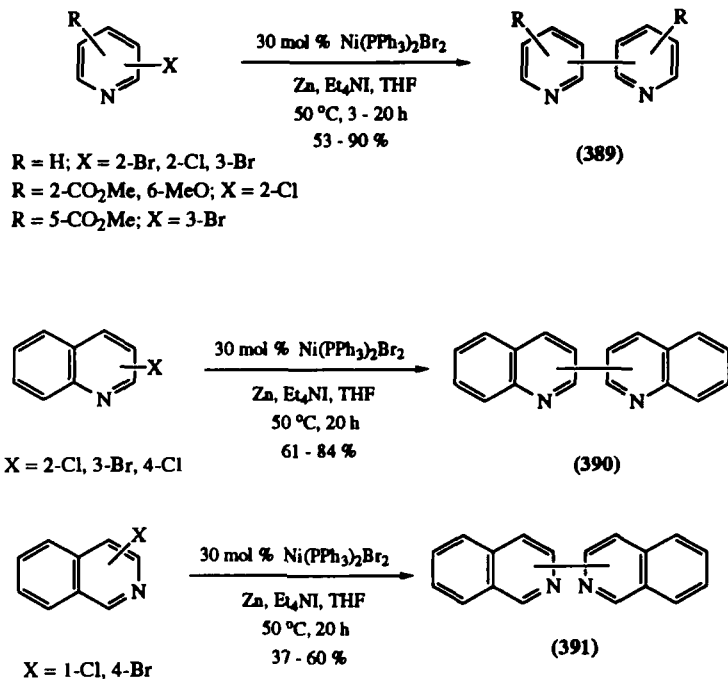
Orellanine, 3,3',4,4'-tetrahydroxy-2,2'-bipyridine bis-*N,N'*-oxide, which is the main toxin of the *Cortinarius Orellanus Fries* mushroom, was synthesized almost at the same time by two groups, both of which



SCHEME 92

used the Zn–Ni protocol for homo-coupling of 2-halogeno-3,4-dimethoxypyridine to the key step intermediate (395). The 2-chloropyridine gave the homo-coupled product (395) in 25% yield (85TL4903), and the 2-bromopyridine gave the homo-coupled product in 75% yield (86TL1475). For the natural-product synthesis, the coupling product was subsequently demethylated under acidic conditions and *N*-oxidized to the toxin orellanine.

With the strongly electron-withdrawing trifluoromethyl as a substituent in 2-chloropyridine, homo-coupling with Zn–Ni protocol in the presence



SCHEME 93

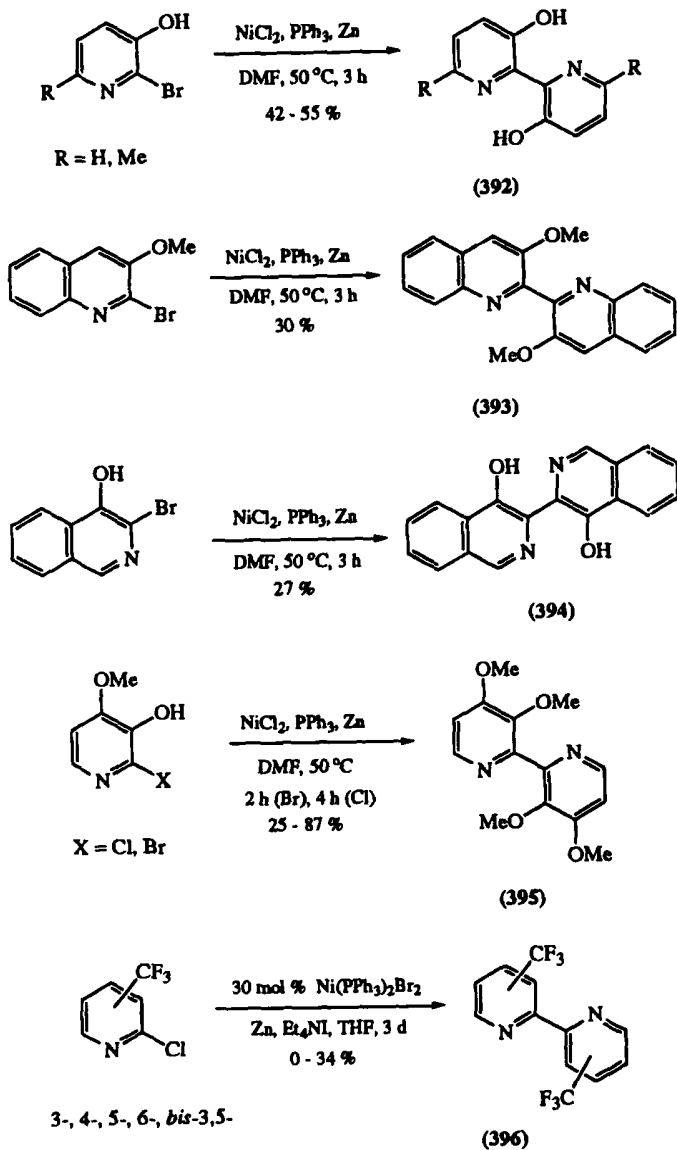
of iodide ions gave ~30% of the 2,2'-bipyridine (396), with the exception of the 3-trifluoromethyl isomer which failed to give the bipyridine. On the other hand, the 3,5-bis(trifluoromethyl) derivative of 2-chloropyridine gave the 2,2'-bipyridine in 33% yield (93SC1929).

Substituted 4-chloropyrimidines are dimerized to 4,4'-bipyrimidines (397) by the same low-valent nickel protocol (93S478).

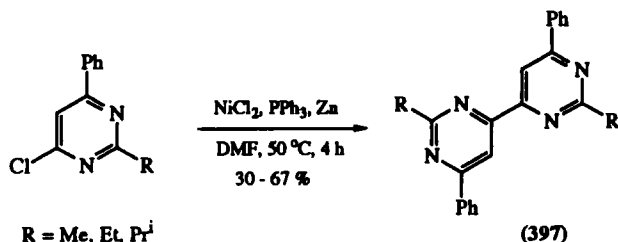
B. HOMO-COUPLING MEDIATED BY OTHER METALS

1. General

The literature on homo-coupling in arenes suggests that a number of metals and metal complexes will be applicable for homo-couplings of heteroarenes. In the heterocyclic reactions described in the previous sections, variable amounts of homo-coupling accompany reactions in which cross-coupling was intended. When the cross-coupling is relatively slow, homo-coupling may become a major pathway.



SCHEME 94



SCHEME 95

The methodologies described for cross-coupling reactions in the previous sections can equally well be used to prepare symmetric biheteroaryls, corresponding to homo-coupling, from the same heterocycle that is compatibly functionalized for the coupling in the same relative position.

2. Halogenoazines

The relatively vigorous reaction conditions required to effect vinyl substitution by heteroaryl halides under the influence of Pd-catalysis may lead to homo-coupling. The dominating reaction path in attempted alkenylations of 4-iodopyrimidines was the formation of 4,4'-bipyrimidines (**19**) (Scheme 4; Section II.A.2). In reactions of 4-iodopyrimidines with a Pd-catalyst at 160°C, near-quantitative yields of the 4,4'-bipyrimidine were obtained (79CPB193). Also, in the reaction of 2-iodo-4-methylquinoline with Pd(OAc)₂ as added catalyst, a major reaction path led to 4,4'-dimethyl-2,2'-biquinoline (Scheme 2; Section II.A.2.) (82CPB3647).

Not unexpectedly, the ligand for the catalyst is important for the reaction path. Early studies of the Ni-promoted reaction of 2-chloroquinoline with Grignard reagents from allyl and benzyl halides using two different phosphine ligands showed that dppe favored homo-coupling, whereas PPh₃ favored cross-coupling (**325**) (Scheme 75; Section III.E.3) (73JHC243). Halogenated azines in the benzenoid positions may also have homo-coupling as major pathway; attempts to effect cross-coupling of 3-iodoquinoline in the Reformatsky reaction gave 3,3'-biquinoline (**279**) as the main product (Scheme 63; Section III.D.2) (85CPB4309).

3. Metalloazines

Metallated azines may also favor homo-coupling rather than cross-coupling. A relevant example is provided by stannylazines in reactions with acid chlorides to form ketones under Pd-catalysis. Considerable

amounts of homo-coupled 3,3'-bipyridine, -isoquinoline, and -quinoline (181) were formed (Scheme 38; Section III.A.3). On the other hand, the conditions constitute a good method for Pd-catalyzed homo-coupling with the stannylazine in the absence of acid chloride (82CPB2003).

Copper-mediated coupling under Ullman conditions was for a long time an important route for the preparation of symmetric biaryls and heteroaryls, as exemplified by the synthesis of 2,2'-bipyridine by heating 2-bromopyridine with finely divided copper (65CA18018). In mixtures of different halogeno substrates, mixtures of symmetric and dissymmetric biheteroaryls are to be expected. This is illustrated by the reaction between 3-iodopyridine and bromonitrobenzenes, where homo-coupling (348, 349) was the dominating reaction path under Ullman conditions; but in the presence of $\text{Pd}(\text{PPh}_3)_4$ the major product was due to cross-coupling (Scheme 80; Section III.F.2.) (84JOC5237; 93TL3421). Homo-coupling can also be effected in reactions of appropriate sulfoxides with Grignard reagents [90AHC(48)1]. This coupling is illustrated by the addition of alkylmagnesium bromide to methyl 2-pyridyl sulfoxides or methyl 2-quinolyl sulfoxide with formation of 2,2'-bipyridines (376) or 2,2'-biquinoline (377) (Scheme 89; Section III.H.2). Alternatively, homo-coupling is achieved from a symmetric biheteroaryl sulfoxide on reaction with an alkylmagnesium halide (87PS123; 89BCJ3848).

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